VOLUME 62 • OVEMBER 1959 • NUMBER 5

OPHTHALMOLOGY

Studies on the Living Cornea in Vitro
Anthony Donn, David M. Maurice, and Nancy L. Mills
I. Method and Physiologic Measurements
II. The Active Transport of Sodium Across the Epithelium

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Morris A. Gordon, William W. Vallotton, and G. S. Croffead

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James E. Miller

Electroretinographic Measurement of the Spectral Sensitivity in Albinos, Caucasians, and Negroes
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Electromyographic Study of Following Movements of the Eye Between Tertiary Positions
Edward Tamler, Arthur Jampolsky, and Elwin Marg

Ocular Pressure Patterns in the Valsalva Maneuver
David A. Rosen and Vida C. Johnston

Studies on Intraocular Effects of the Orbital Parasympathetic Pathway
Mansour F. Armaly

Progressive Multifocal Leukoencephalopathy
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Stain Permeability and Ultrastructure of the Corneal Endothelium
J. S. Speakman

Bilateral Melanoma of the Choroid Associated with Leukemia Meningioma
Herbert Wiesinger, G. W. Phipps, and DuPont Guerry III

Aneurysm of the Anterior Cerebral Artery
Frank R. Shlossberg

Neuro-Ophthalmology
John Woodworth Henderson

Correspondence

Obituary: Bernard Samuels

News and Comment

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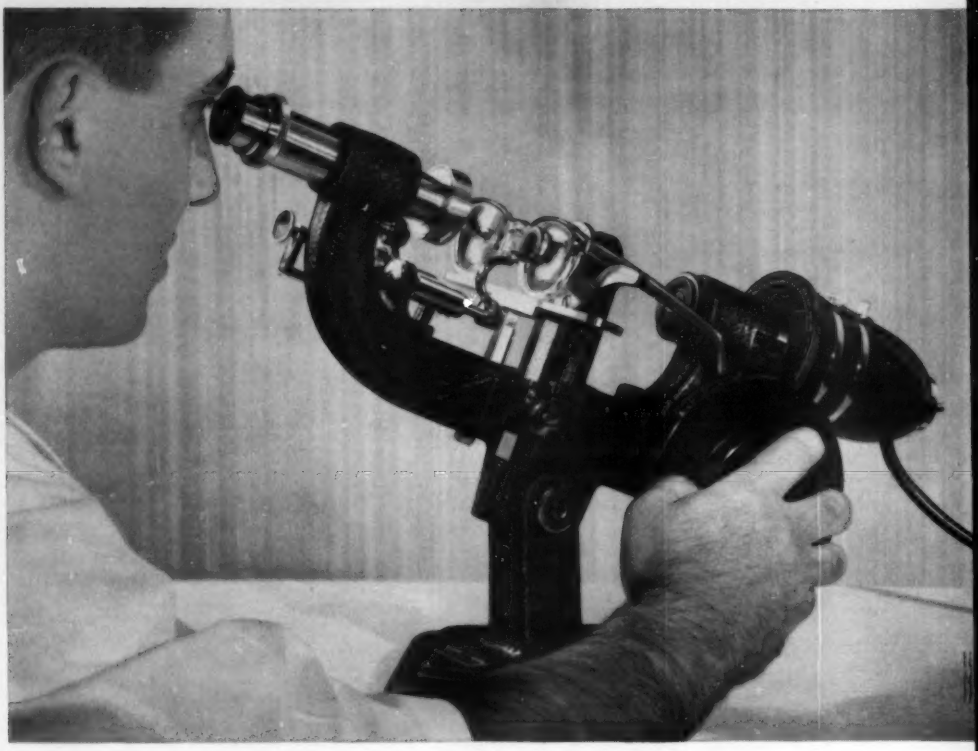

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TABLE OF CONTENTS

VOLUME 62 NOVEMBER 1959 NUMBER 5

ORIGINAL ARTICLES

PAGE

Studies on the Living Cornea in Vitro
Anthony Donn, M.D., New York; David M. Maurice, Ph.D., London, England, and Nancy L. Mills, B.S., New York
I. Method and Physiologic Measurements 741
II. The Active Transport of Sodium Across the Epithelium 748

Corneal Allescheriosis
Morris A. Gordon, Ph.D.; William W. Vallotton, M.D., and G. S. Croffead, M.D., Charleston, S.C. 758

Lens Surgery in Marfan's Syndrome
Daniel Kravitz, M.D., Brooklyn 764

Pupillary Escape in Disease of the Retina or Optic Nerve
Paul Levatin, M.D., Oakland, Calif. 768

The Antibacterial Property of Vitreous
Howard Reed, M.B., M.S. (Lond.), and George Tushingham, A.I.M.L.T., Winnipeg, Man., Canada 780

Prevention of Herpes Corneae in Rabbits
Joseph V. M. Ross, M.D., Berwick, Pa. 782

Mutations of the Retinal Pigment Cells in a Case of Pseudoglioma
Y. Dayal, M.S., and F. C. Rodger, Ch.M., Aligarh, India 785

The Electromyography of Vergence Movement
James E. Miller, M.D., St. Louis 790

Electroretinographic Measurement of the Spectral Sensitivity in Albinos, Caucasians, and Negroes
E. Dodt, M.D.; Richard M. Copenhaver, M.D., and R. D. Gunkel, O.D., Bethesda, Md. 795

Electromyographic Study of Following Movements of the Eye Between Tertiary Positions
Edward Tamler, M.D.; Arthur Jampolsky, M.D., San Francisco, and Elwin Marg, Ph.D., Berkeley, Calif. 804

Ocular Pressure Patterns in the Valsalva Maneuver
David A. Rosen, M.D., and Vida C. Johnston, P.H.N., Kingston, Ont., Canada 810

Studies on Intraocular Effects of the Orbital Parasympathetic Pathway
Mansour F. Armaly, M.D., Iowa City 817

Progressive Multifocal Leukoencephalopathy
J. Lawton Smith, M.D., Boston 828

Progressive Dystrophic External Ophthalmoplegia with Abiotrophic Fundus Changes
Jon C. Thorson, M.D., and William E. Bell, M.D., Iowa City 833

Ocular Rigidity
Victor Goodside, M.D., New York 839

Inheritance of Retinoblastoma in Ohio
Madge T. Macklin, M.D., Columbus, Ohio 842

Angioid Streaks and Sickle Cell Anemia
David Paton, M.D., Bethesda, Md. 852

Diabetic Retinopathy and the Pituitary
Eugene J. Ranke, M.D., Chicago 859

Nystagmus Retractorius
J. Lawton Smith, M.D.; Irving Zieper, M.D.; Andrew J. Gay, M.D., and David G. Cogan, M.D., Boston 864

Abnormal Serum Proteins and Retinal Vein Thrombosis
Harold F. Spalter, M.D., New York 868

Stain Permeability and Ultrastructure of the Corneal Endothelium
J. S. Speakman, M.D., Toronto 882

Bilateral Melanoma of the Choroid Associated with Leukemia Meningioma
Herbert Wiesinger, M.D.; G. W. Phipps, M.D., and DuPont Guerry III, M.D., Richmond, Va. 889

CASE REPORTS

Aneurysm of the Anterior Cerebral Artery
Frank R. Shlossberg, M.D., Haverhill, Mass. 894

ANNUAL REVIEWS

Neuro-Ophthalmology
John Woodworth Henderson, M.D., Ann Arbor 895

(Continued On Ad Page 8)

A. M. A.
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VOLUME 62 NOVEMBER 1959 NUMBER 5

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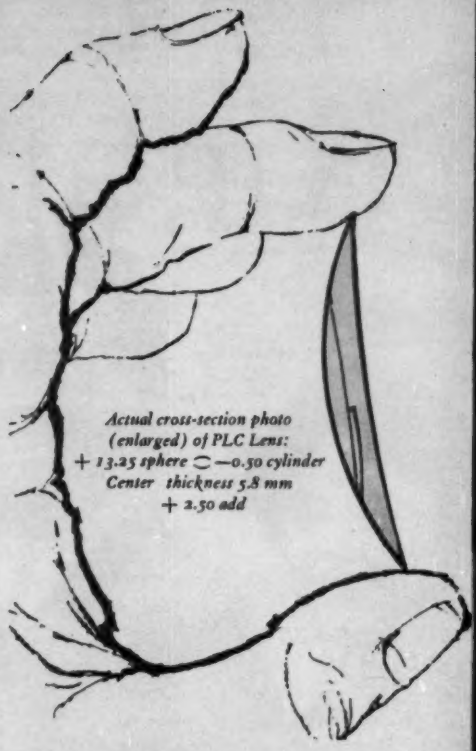

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TABLE OF CONTENTS (Continued)

CORRESPONDENCE

The Occurrence of Glaucoma Following Occlusion of the Central Retinal Artery
K. W. Ascher, M.D., Cincinnati 917

Removing Superficial Corneal Plastic Foreign Bodies
T. D. Duane, M.D., Bethlehem, Pa. 917

The Maddox-Rod Phenomenon
G. H. Giles, O.B.E., London, England 917
Harry Eggers, M.D., New York 917

After-Images and Ocular Muscle Proprioception
Paul W. Miles, M.D., St. Louis 918
Martin J. Urist, M.D., South Haven, Mich. 918

The Use of a Mohair Brush in Intraocular Surgery
Ray H. Nielsen, M.D., North Hollywood, Calif. 918

OBITUARIES

Bernard Samuels, M.D. 920

REGULAR DEPARTMENTS

News and Comment 923

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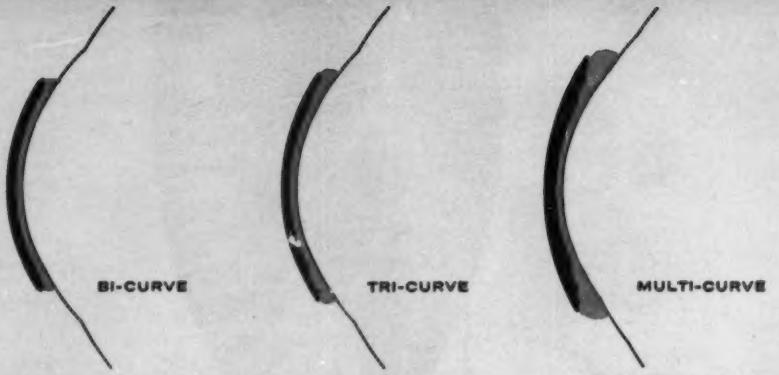

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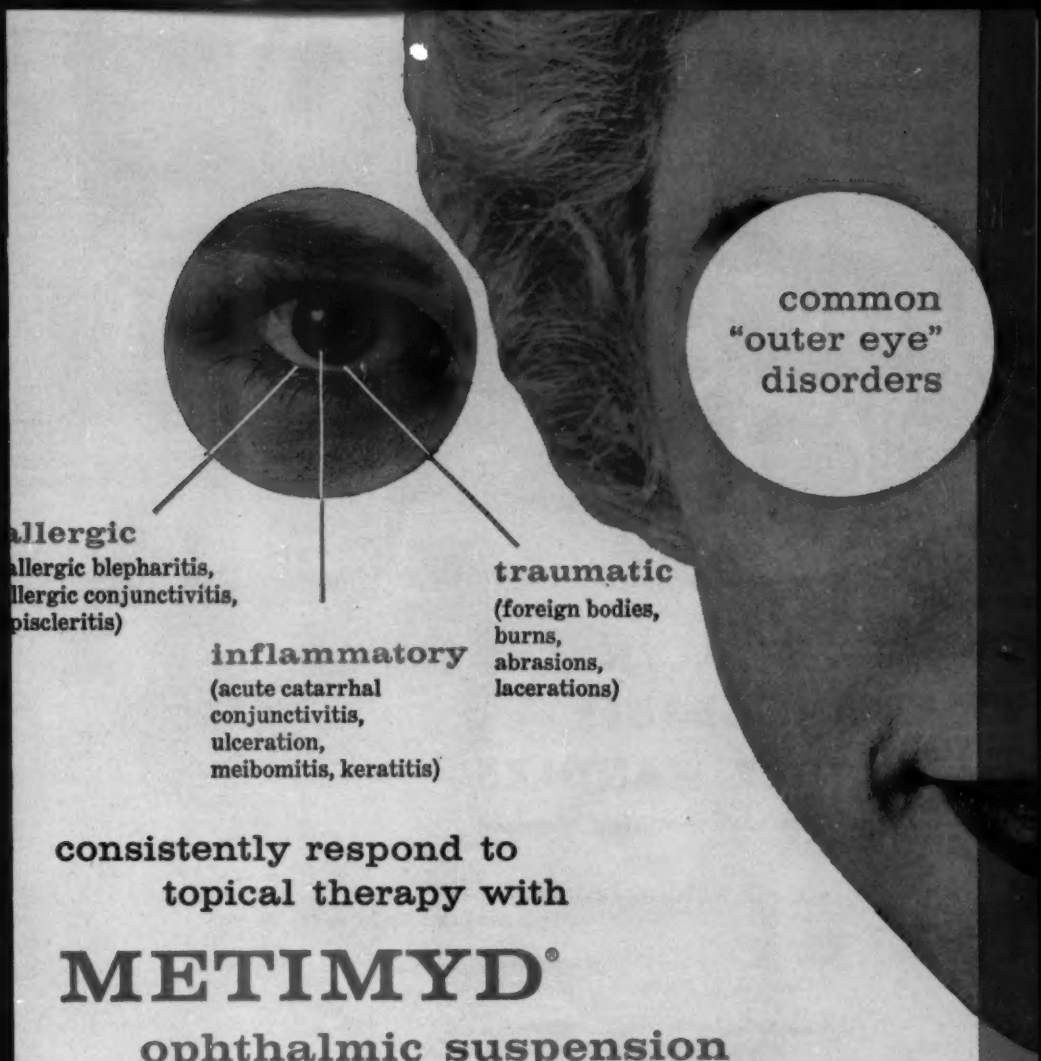

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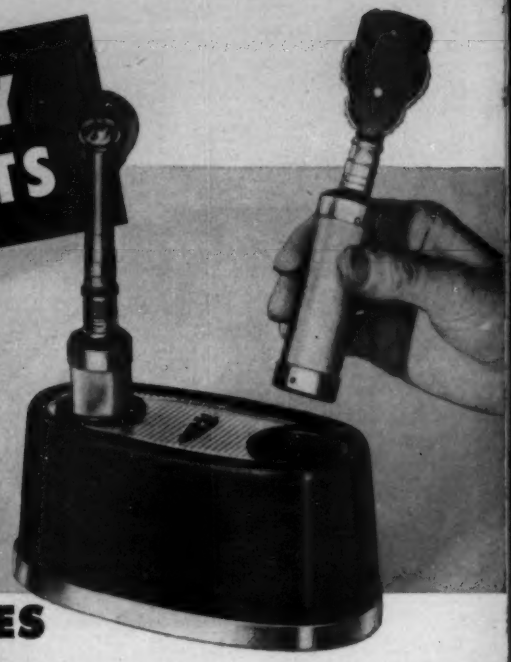

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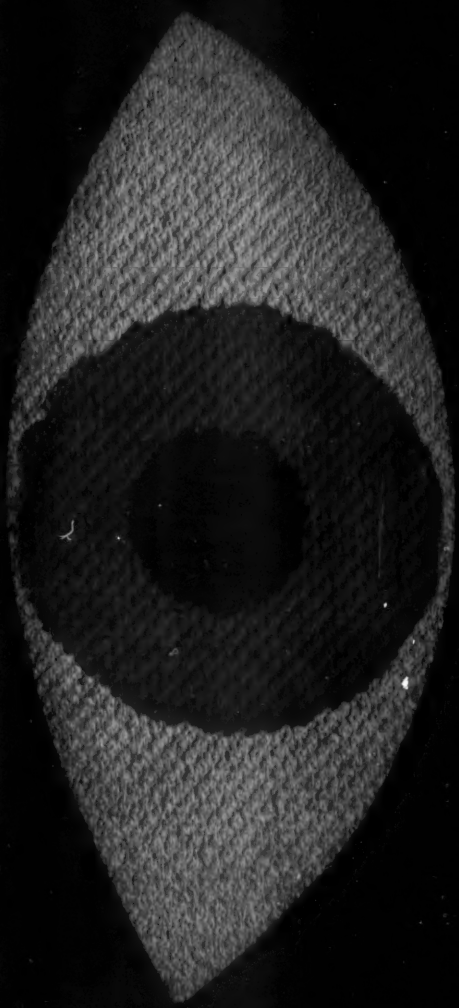

References: (1) Perkins, E. S. **Practitioner 178**:525, 1957. (2) Smith, C. H. **Eye, Ear, Nose & Throat Month. 34**:580, 1955. (3) Blakiston's New Gould Medical Dictionary, ed. 2. New York, McGraw-Hill Book Company, Inc., 1956, p. 945. (4) Ostler, H. B. & Braley, A. E. **J. Iowa M. Soc. 44**:427, 1954.

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References: Leopold, I. H., et al.: A.M.A. Arch. Ophth. *58*, 363(1957); Krishna, N. & Leopold, I. H.: ibid, *62*, 309(1959); Krishna, N., Leopold, I. H. & Lehman, R. A., Effects of Anticholinesterase Agents on the Blood Cholinesterase Levels of Normal and Glaucoma Subjects: Am. Ophth. Soc., Hot Springs, May 29, 1959; Becker, Bernard, et. al.: Am. J. Ophth. *47*, 635(1959); ibid. *48*, 313(1959); Lawlor, R. C. & Lee, P. F., Use of Phospholine Iodide in the treatment of Glaucoma: N. E. Ophth. Soc., Boston, April 16, 1958; Seward, W. J. & Albert, D. G., Use of Phospholine Iodide in the Treatment of Glaucoma: Episcopal Hospital, Washington, May 3, 1958; Drance, S. M., Effects of Phospholine Iodide on the Intraocular Pressure in Man: Univ. Saskatchewan, A.M.A. Arch. Ophth., in press.; Miller, J. E., Comparative Study of Miotics in Accommodative Esotropia: Washington Univ., St. Louis: Am. J. Ophth., in press.; Giardini, A. et. al., Sul Trattamento del Glaucoma Mediante Phospholine Iodide: Boll. d'Oculista, in press.

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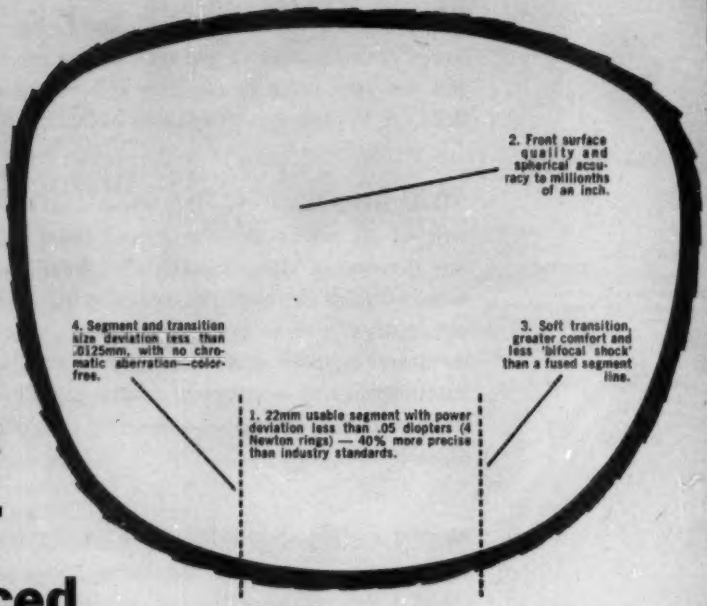
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This was the case last October when we offered to exchange all laboratory stocks of Younger Seamless Lenses manufactured prior to October, 1958.

A major breakthrough in quality and precision, achieved after twelve years of constant and continuous development, research and engineering, has permitted the manufacture of a vastly improved, seamless dual-field lens with a full 22mm usable segment with less than .05 diopter power deviation; a front surface accuracy to millionths of an inch and a segment-size deviation of less than .0125mm!

Because of the unsurpassed quality of the new Younger-22 Seamless Lens, the decision was made to replace all existing Younger stocks.

We are grateful to the thousands of professional men who have continued to prescribe the very acceptable Younger Seamless Lens during the period of its development; *they* know today how much better the new lens is!

If you haven't prescribed a Younger Lens since this past October, you are missing one of the most significant advances in lens manufacture of the past decade.

Remember: you do not take the slightest risk when you do so, for if the patient cannot wear Youngers for any reason, your independent supplier will replace it with a fused bifocal of your choice at no additional cost.

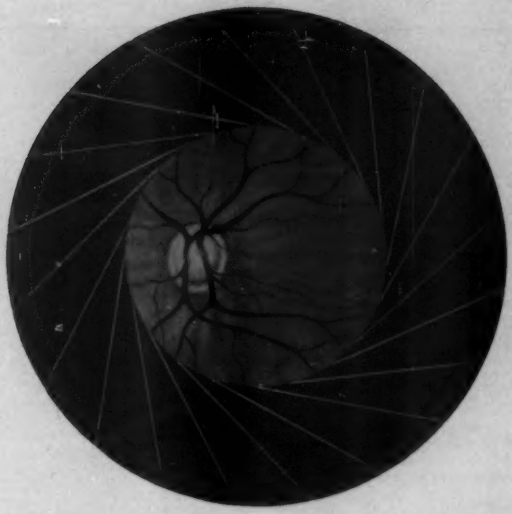
Write on your letterhead for a sample of the vastly improved Younger-22 Seamless Lens. There is no charge, but please give us the name of your independent supplier.

YOUNGER

1829 SOUTH MAIN STREET
LOS ANGELES 15, CALIF.

Y-29

INTERESTED IN A SIMPLE, DIRECT PRESENTATION OF THIS UNUSUAL LENS TO YOUR PATIENTS? WRITE FOR THE STORY!



NOW...DISTINCT FUNDUSCOPIC OBSERVATIONS
CYCLOMYDRIL™...FOR MYDRIASIS
FAST...PROFOUND...WITHOUT CYCLOPLEGIA

Fundoscopic examination is easy and accurate—therapeutic mydriasis profound and effective—through the use of New CYCLOMYDRIL.™[2] Even in the most darkly pigmented iris, a dramatic pupillary dilation begins upon instillation. This profound mydriasis is resistant to bright light *but readily reversible in an hour or less with a miotic.*

Mean Increase in Pupil Size
30 Minutes after Instillation[1]

brown or hazel eyes	3.15 mm.
dark brown (Negro) eyes	3.50 mm.
blue, gray or green eyes	4.38 mm.

The combined action of phenylephrine—an adrenergic mydriatic of choice[2] and Cyclogyl®—a potent anticholinergic mydriatic (in a concentration without cycloplegic effects) produces a pupillary dilation greater than that obtained by either drug alone. Cyclomydril is well tolerated—no significant change in ocular tension or other serious side effects.

Indications and Dosage: In fundoscopy—one drop in each eye.
In treatment of iritis, iridocyclitis, keratitis, choroiditis, posterior synechiae, ocular trauma and after removal of cataracts or other ocular surgery—one drop every 6-8 hours.
May be used for refraction in certain patients who have little or no accommodation. (Cyclogyl® is required when both cycloplegia and mydriasis are indicated.)

Composition: Cyclogyl® (cyclopentolate hydrochloride 0.2%, phenylephrine hydrochloride 1.0% with PVP (polyvinylpyrrolidone) in a sterile, buffered ophthalmic solution.
Available in 2 ml. and 7.5 ml. dropper bottles.

Samples and literature available on request.

1. Everett, B. ... Mellow, M. M., and Phillips, C. I. To be published. 2. Duquesnoy, R. P. in Drill, V. A., Pharmacology in Medicine, McGraw-Hill Book Company, Inc. New York, 1954, p. 18-26.

Pharmaceutical Co. / Division of ...

CYCLOMYDRIL

The ARMORLITE LENS co., inc.
BIN 1200 • PASADENA, CALIFORNIA
MUrray 1-8193 • SYcamore 8-1216

AVAILABILITY CHART OF CRYSTAL-WHITE CORRECTED CURVE LENSES

100% PURE HARD RESIN

UNCUT STOCK LENSES 55 mm. ROUND

Spheres

Plano to ± 6.00

+ ⊃ + Compounds

SPHERE	CYLINDER
+ .25 to + 4.00	+ .25 to + 3.00
+ 4.25 to + 5.75	+ .25 to + 2.00

(Total + power not to exceed 6.00 D.)

Plano Cylinders

+ .12 to + 3.00

— ⊃ + Compounds

SPHERE	CYLINDER
— .25 to — 6.00	+ .25 to + 3.00

PRESCRIPTION SERVICE

Spheres + and —

Plano to 16.00

Plano + Cylinders

.25 to 4.00

+ ⊃ + and — ⊃ + Compounds

Powers beyond stock range available to + or — 15.00 with Cyl. to + 4.00 D.
(Compounds above + 10.00 D. supplied with Cyl. powers to + 3.00 D. only.)
Powers beyond these available on request.

Prism

.50 △ to 5.00 △

Bifocals

Available in 21 mm. one-piece segment. Segments are free from chromatic aberration and as inconspicuous as any ever produced.

Plano to — 2.00 sph. ⊃ + cyl. .25 to 4.00; adds + 1.00 to + 2.50.
— 2.25 to — 10.00 sph. ⊃ + cyl. .25 to 4.00; adds + 1.50 to + 2.50.
+ .25 to + 2.00 sph. ⊃ + cyl. .25 to 4.00; adds + 1.25 to + 2.50.
+ 2.25 to + 8.75 sph. ⊃ + cyl. .25 to 4.00; adds + 1.00 to + 3.00.
+ 9.00 to + 13.50 sph. ⊃ + cyl. .25 to 3.00; adds + 2.00 to + 3.00.
+13.75 to + 16.00 sph. ⊃ + cyl. .25 to 3.00; adds + 2.50, 3.00.

Total distance power not to exceed + 16.50

Uniform Density Tints

Flesh
Light
Medium
Dark

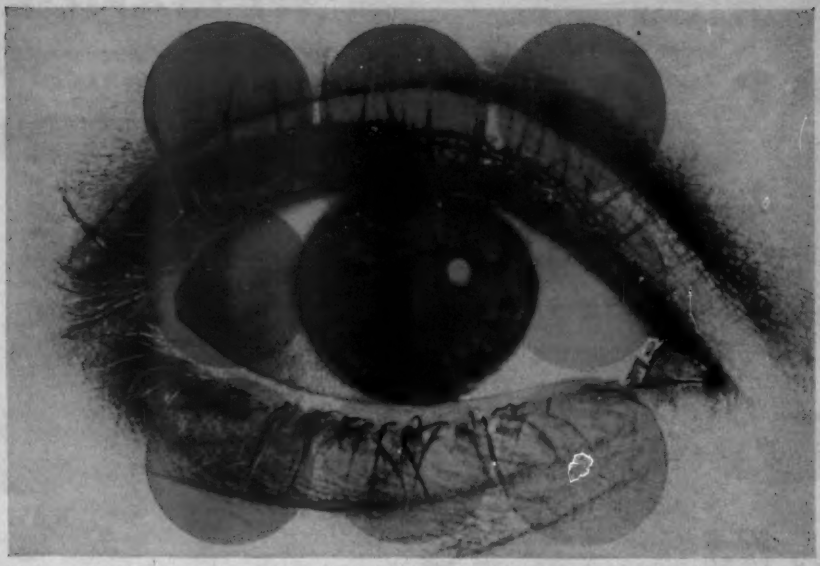
Green
Light
Medium
Dark

Armorgrey
Medium
Dark

Armortan
Yellow
Blue

EXTRAS AVAILABLE

Ultraviolet absorbing lenses (with or without color)
Lenticular (minus only)
Industrial thickness (3 mm.)
Myo-disc
Powers beyond listed range
Special base curves
Prism for decentration
Lenses larger than 55 mm.



FOR EYES OF EVERY HUE... CYCLOGYL® FOR CYCLOPLEGIA

NEW... FOR THE DARK BROWN OR BLACK IRIS... CYCLOGYL 2% WITH PVP— the special soothing base containing PVP (polyvinylpyrrolidone) permits use of a higher concentration, effective even in the most darkly pigmented iris.

FOR THE BROWN OR HAZEL IRIS... CYCLOGYL 1%

FOR THE BLUE, GRAY OR GREEN IRIS... CYCLOGYL 0.5%

VALUABLE TIMESAVING – effective within 30 minutes – rapid recovery when a miotic is used.*

MAXIMAL SAFETY "... no significant variation of intraocular tension has been reported ... does not produce any undesirable local or systemic effects following repeated instillation... it is relatively nonirritating and nonsensitizing... animal studies show low toxicity..."[1]

INDICATIONS: Refraction. When both cycloplegia and mydriasis are desired in treatment of iritis, iridocyclitis, keratitis and choroiditis – preoperatively for cataract or other appropriate surgery. (Cyclomydril™ [Cyclogyl 0.2% with phenylephrine 1%] is indicated for diagnostic procedures and therapy requiring only mydriasis).

AVAILABILITY:

New Cyclogyl 2%	7.5 ml. dropper bottle, 2 ml. dropper bottle (prescription size)
Cyclogyl 1%	15 ml. dropper bottle, 2 ml. dropper bottle (prescription size)
Cyclogyl 0.5%	15 ml. dropper bottle

SAMPLES AND LITERATURE AVAILABLE ON REQUEST

*When a miotic cannot be used, recovery occurs within 24 hours.

1. New and Nonofficial Drugs; J. B. Lippincott Company, Philadelphia, 1958, p. 243.

Schieffelin & Co./Since 1794
Pharmaceutical and Research Laboratories
New York 3, N.Y.

CYCLOGYL®
(cyclopentolate hydrochloride, Schieffelin)

THE PERFECT COMBINATION

for Examination, Treatment and Contact Lens Work

"THE SPECIALIST" CHAIR

Appropriately named "The SPECIALIST," this RELIANCE chair —created expressly for eye examination and treatment— allows the doctor, when seated, to work close to his patient, without stretching or leaning. Features in addition: Rapid patient positioning, smart appearance trouble-free durability.

Manufacturers since 1898

F. & F. **KOENIGKRAMER CO.**
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RELIANCE

Model 1225K ADJUSTABLE INSTRUMENT TABLE

For fast, effortless positioning of diagnostic instruments. Mechanism counterbalances the weight of any instrument weighing between 12 and 60 lbs. Depress the foot pedal—raise or lower as desired. Release the pedal and table locks in place. Raises from 26½" to 35".

Model 1225K/C—same as above but with casters. Raises from 28½" to 37".

(pat. app. for)

See all Reliance products at your authorized dealer or write for brochure.

For the Extra Refracting or Treatment Room

CHAIR: Upholstered, reclining, adjustable headrest, can be raised or lowered by large ball-bearing wheel; can be locked in any position; elevation 18 to 24". $155.00 in brown, green or black. Other colors available at $5.00 extra.

CABINET: Stainless steel covered; wall mounted or floor model; with or without electrical equipment. Can be furnished with pull-out writing shelf and horizontal drawers on roller bearings. $115.00 to $290.00

STOOL: Upholstered; with or without backrest; ballbearing casters. $20.00—$26.00 in brown, green or black. Other colors available at $1.00 extra.

LIGHT: Can be mounted on Chair or wall; vertical movement by means of self-adjusting clutch on bar, lateral and anterior-posterior movement by means of goose-neck. $22.00

LIGHT SHIELD: For standard 100 watt lamp $5.00

STAINLESS STEEL TISSUE CONTAINER: $3.00

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Established over 30 years

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make protection a part of every prescription

Every lens must withstand the impact of a ⅝" steel ball dropped from a height of more than 4 feet.
THESE ARE GENUINE
HARDRx*
SAFETY LENSES
* prescribed for that important margin of safety for your eyes

BENSON'S HARDRx SAFETY LENSES!

Eyes worth correcting are worth protecting. Every one of your patients *deserve* maximum safety from dangerous and costly lens breakage. Benson's HARDRx safety lenses — ground to a formula-determined thickness and scientifically heat treated — are toughened to resist impact.

To impress on your patients that you've prescribed the unexcelled in lenses for them, the identifying tag shown at left is attached to each pair of genuine HARDRx lenses. Your patients will appreciate your thoughtfulness in prescribing this extra protection . . . and will tell their friends of your quality service.

Join the growing number of doctors who specify HARDRx regularly. Remember: HARDRx prescriptions receive the same prompt handling.

1913-1959 . . . Our 46th year

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specialists in prescription optics since 1913

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3 ophthalmic products with **distinctive advantages...**

- their wide-spectrum bactericidal activity includes *ALL clinically isolated strains of Pseudomonas aeruginosa*, a serious invader noted for the rapidity of its destructive powers.
- their component antibiotics rarely sensitize.

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brand Polymyxin B-Gramicidin-Neomycin

ANTIBIOTIC OPHTHALMIC SOLUTION

Available in bottles of 10 cc. with sterile dropper.

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a scientific corner

FOR INFORMAL DISCUSSION OF YOUR OPTICAL PROBLEMS

The House of Vision Inc.

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DES MOINES • MASON CITY • SIOUX CITY • AMES • DAVENPORT • NEWTON
MILWAUKEE • MINNEAPOLIS

WHEN IS A 12.00 DIOPTER LENS NOT A 12.00 DIOPTER LENS?

Answer: When you refract the patient at 15 mm. and your optician fits the finished glasses at 9 mm.

Because the patient you refract at 15 mm. requires a 13.00 diopter lens from the optician when it is fitted at 9 mm.

We assume all ophthalmologists know that the vertex distance is important in all corrections, both plus and minus, above 5.00 diopters. And if you want the best results in those strong corrections, you owe it to your patient and to your optician to measure the vertex distance of the principal refracting lens from your patient's eyes and note it on your prescription.

Do you have a distometer and a distometer conversion scale? They are available from The House of Vision or from your local optician—and, incidentally, the distometer conversion scale is a must for anyone fitting contact lenses, as it is a permanent plastic rotary slide rule showing the conversion of any power lens from 5.00 diopters to 25.00 diopters, both plus and minus, for any changing vertex distance from 25 mm. to zero.

Actual size—5⅞" diam.

The price of the plastic distometer slide rule conversion scale is only **$3.25.**
The price of the distometer and conversion scale complete is **$13.25.**

"if it's a lens problem, let's look at it together"

THE HOUSE OF VISION—MAKERS OF PRESCRIPTION GLASSES FOR THE MEDICAL PROFESSION—WILL BE HAPPY TO FILL *YOUR* PRESCRIPTIONS.

LEDERLE INTRODUCES....

a masterpiece

greater antibiotic activity

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the activity of tetracycline against susceptible organisms. (*Activity* level is the basis of comparison—not quantitative blood levels—since action upon pathogens is the ultimate value.*) Provides significantly higher serum activity level . . .

with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectru antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents

unrelenting peak antimicrobial attack

The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

DECLO

Demethylchlortetracycline Lederle

# of antibiotic design

plus
"extra-day"
activity

FOR PROTECTION AGAINST RELAPSE

DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline... for greater physician-patient benefit

in the distinctive, dry-filled, duotone capsule

immediately available as:
DECLOMYCIN
Capsules, 150 mg.,
bottles of 16 and 100.
Adult dosage: 1 capsule
four times daily.

MYCIN®

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a Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York

storz Surgical Instruments

Electro-Keratotome

CASTROVIEJO

For the Dissection of Lamellar Grafts.

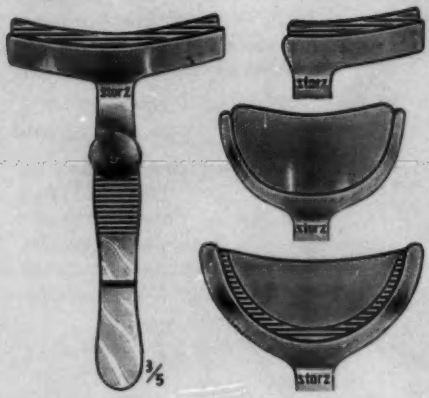
Procedure is shortened, and minimally traumatized grafts of even thickness and as large as permitted by the donor's eye are obtained, a result difficult to achieve by older methods, especially with larger grafts.

- **Small enough to observe the donor eye for which it is used only.**
- **Edge of cutting blade visible through open roller guards, enabling surgeon to start and complete graft at exact margins. Uses small, disposable, double-edged razor blade. Simple mechanism.**
- **Shims are provided in thickness of 0.1, 0.2, 0.3, 0.4 and 0.5 mm., permitting grafts from 0.1 to 0.5 mm. thick. This method so accurately controls the thickness that two grafts of 6 mm. diameter have been removed from a single donor eye.**

INSTRUMENT ALSO USEFUL FOR cutting buccal mucous grafts for plastic repair in cases of symblepharon or extensive scarring of the conjunctiva. The mucous membrane can be taken from the buccal surface of lip or cheek. It cuts the grafts so thin that they need no further thinning, which was impossible with previous instruments.

Head of instrument is Stainless Steel. Motor is rotary type, AC or DC, 110 V.

Ref., Am. Journal Ophth., Feb. 1959



CLAMPS

E-2961 through E-2965 are used with E-2950 Electro-Keratotome for cutting of buccal mucous grafts. Prices upon Request.

E-2950 Electro-Keratotome, CASTROVIEJO: with one dozen blades, footswitch and Norelco motor... **$176.00**

E-2952 Extra Blades for **E-2950** per doz. ...**$1.50**

- **CLAMPS**

E-2961 Clamp, Lip, CASTROVIEJO: "T" shape
E-2962 Clamp, Lip, CASTROVIEJO: right
E-2963 Clamp, Lip, CASTROVIEJO: left
E-2964 Clamp, Cheek, CASTROVIEJO: small
E-2965 Clamp, Lip, CASTROVIEJO: large

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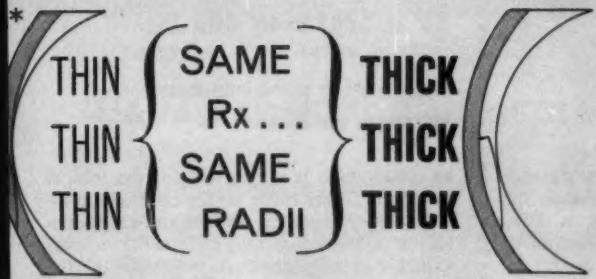
How you can reduce the weight... reduce the thickness... for your "uniform-density Rx" patients:

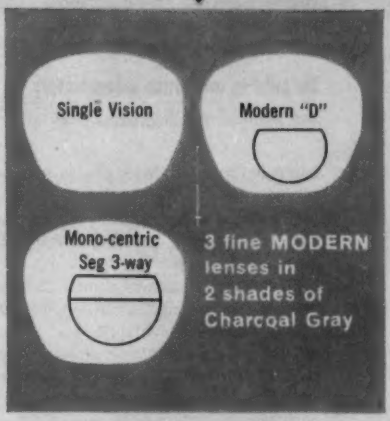
Rx for over -4.50 or +3.00
Modern's Uniform-Density
2-way and 3-way lenses

Rx UNIFORM-DENSITY "Charcoal Gray" in

"*Charcoal Gray* LIGHT"

"*Charcoal Gray* **DARK**"





*odern's Uniform-Density D-22 s its AKRO seg threshold- elded into the convex surface the "Charcoal Gray" cover ns.

All other uniform-density bifocals use a regular white bifocal blank, to which is added the extra weight and thickness of colored cover lens.

*Pat. appld. for.

Another modern idea from... **MODERN OPTICS** *Houston, Texas*
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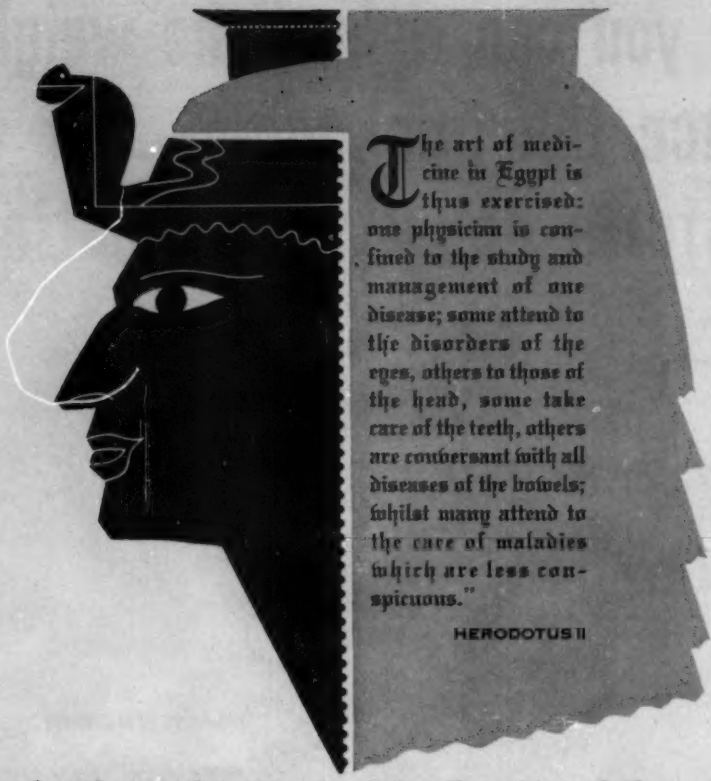

The art of medicine in Egypt is thus exercised: one physicim is confined to the study and management of one disease; some attend to the disorders of the eyes, others to those of the head, some take care of the teeth, others are conversant with all diseases of the bowels; whilst many attend to the cure of maladies which are less conspicuous."
HERODOTUS II

Today...for those who attend to the disorders of the eyes...

Prednefrin®

ophthalmic suspension

for mild to moderate inflammatory and allergic eye disorders

PREDNEFRIN—a formula for unsurpassed effectiveness—in the topical treatment of ophthalmic inflammatory reactions, is indicated whenever the repository effect of a "solution like" suspension is desired. PREDNEFRIN provides a multidimensional approach for unexcelled objective and subjective effectiveness with the anti-inflammatory action of *prednisolone 0.12%*, the decongestant effectiveness of *phenylephrine 0.12%* and the soothing, lubricating properties of *methylcellulose 0.12%*.
SUPPLIED: 5 cc. plastic bottles.

Prednefrin S®

ophthalmic solution

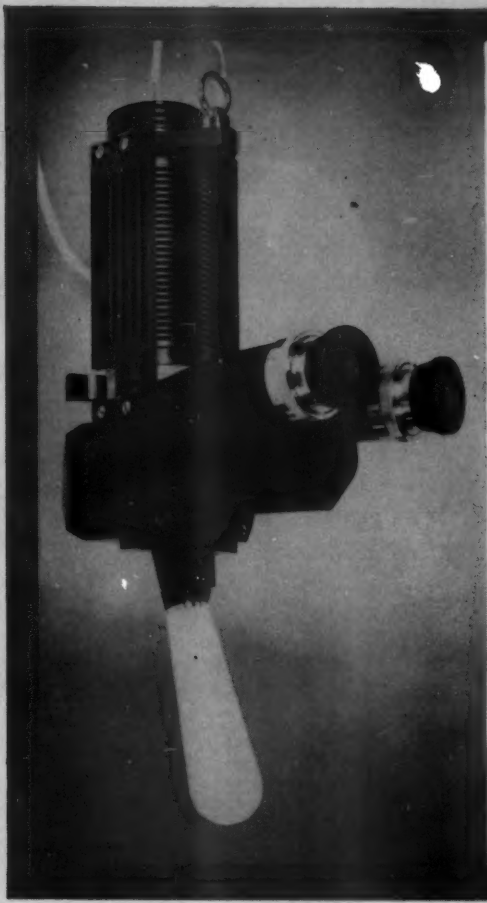
for moderate to severe inflammatory and allergic eye disorders

PREDNEFRIN S is unexcelled for the topical treatment of the more severe ophthalmic inflammatory condition. Potent anti-inflammatory action *(prednisolone alcohol 0.2%)* plus valuable decongestant action *(phenylephrine 0.12%)*. PREDNEFRIN S, *a special solution*, assures the patient of a uniform concentration, with virtual freedom from stinging or burning on instillation or irritation throughout the course of therapy.
SUPPLIED: 5 cc. plastic dropper bottles.

ALLERGAN CORPORATION

Los Angeles 17, California

APPS-1



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newest model
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HEINE GONIOSCOPE

In our opinion this is the finest Gonioscope on the market. It's easier to handle, has better, more brilliant illumination.

- **Prefocused, brilliant, air cooled light source.**
- **Precision German optics — 6 times magnification.**
- **Rotating slit with easy fingertip control.**
- **Adjustable P. D.**
- **Modern design engineered for superb performance.**

AVAILABLE FOR IMMEDIATE DELIVERY!

Heine Gonioscope (as illustrated) Catalog No. X25-PI	**$325.00***
Heine Gonioscope complete with pulleys, counterweight and nylon cord, Catalog No. X25	**$360.00***

** Prices include 5 amp. 6 volt transformer.*

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ZOLYSE™

alpha-chymotrypsin with BALANCED SALT SOLUTION, ALCON

in CATARACT SURGERY

ZOLYSE (alpha-chymotrypsin with BALANCED SALT SOLUTION, ALCON) lyses the zonules, facilitates delivery of the lens and minimizes such dangers as capsular rupture, loss of vitreous, traumatic iridocyclitis and detachment of the retina.

The BALANCED SALT SOLUTION, ALCON, which is furnished as a diluent and for lavage purposes, "offers less cytotoxic effect to the intraocular tissues than does normal saline diluent."[1] It has been recently demonstrated that frequent irrigation with saline results in swelling of the corneal stroma from alteration of the mucopolysaccharides of the cornea."[2]

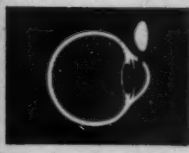
ZOLYSE reduces operative and post-operative complications.

ZOLYSE is well tolerated in patients over 20.

Each ZOLYSE unit contains one vial of 750 units of lyophilized alpha-chymotrypsin and one 10 cc vial of BALANCED SALT SOLUTION, ALCON, as the diluent and for irrigating the eye.

[1]Girard, Louis J., and Neely, Wanda: "The Evaluation of Zolyse in Cataract Extraction", Research Report No. 11, Alcon Laboratories, Inc., 1959.

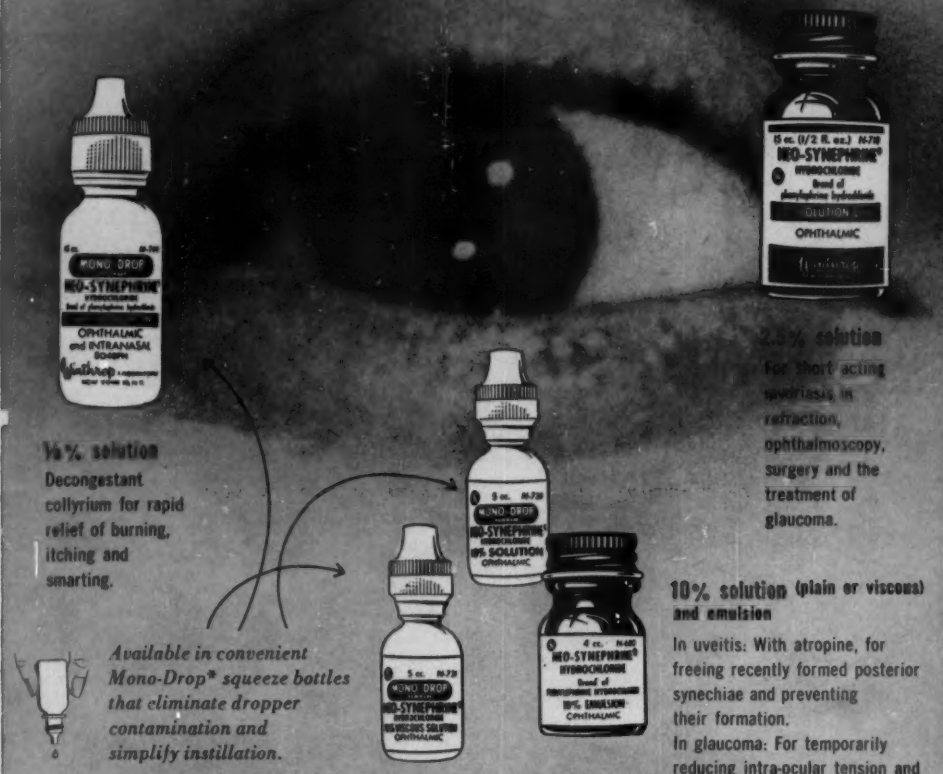
[2]Boyd, Benjamin F.: Enzymatic Zonulysis, Highlights of Ophth., vol. III, no. 4, pg. 70, 1959.



Alcon ALCON LABORATORIES, Inc.
FORT WORTH, TEXAS

when the eyes have it

There are five dosage forms of Neo-Synephrine hydrochloride especially formulated for vasoconstriction and mydriasis in ophthalmologic conditions.



2.5% solution
For short acting mydriasis in refraction, ophthalmoscopy, surgery and the treatment of glaucoma.

½% solution
Decongestant collyrium for rapid relief of burning, itching and smarting.

Available in convenient Mono-Drop squeeze bottles that eliminate dropper contamination and simplify instillation.*

10% solution (plain or viscous) and emulsion
In uveitis: With atropine, for freeing recently formed posterior synechiae and preventing their formation.
In glaucoma: For temporarily reducing intra-ocular tension and for performing the provocative test for angle block.
For use in surgery.

NEO-SYNEPHRINE®
Hydrochloride

wide application in ophthalmology

Winthrop LABORATORIES • NEW YORK 18, N. Y.

*Mono-Drop, trademark

Neo-Synephrine (brand of phenylephrine), trademark reg. U.S. Pat. Off.

A.M.A. ARCHIVES OF
OPHTHALMOLOGY

Studies on the Living Cornea in Vitro

I. Method and Physiologic Measurements

ANTHONY DONN, M.D., New York; DAVID M. MAURICE, Ph.D., London, England, and NANCY L. MILLS, B.S., New York

In order to determine if ions are actively transported across the corneal epithelium or endothelium, it was decided to excise the cornea and mount it between two chambers so that the composition of the fluid on the two sides could be regulated and analyzed. This arrangement lends itself to the direct measurement of ion fluxes. The critical problem in this method, however, is to keep a dissected cornea functioning normally in vitro. The present work describes a technique of maintaining an excised rabbit cornea alive for up to eight hours while measuring several of its physiologic properties.

Materials and Methods

Large adult rabbits were killed with intravenous Nembutal (pentobarbital) and the anterior segment of one eye was excised 2 mm. posterior to the limbus within one minute of death. The tissue was held by its scleral lip and immersed in a solution similar in composition to aqueous humor * [1] where the lens and iris were dissected away. Throughout the preparation great care was taken to avoid touching either surface of the cornea with a solid object and, as far as possible, to prevent the tissue wrinkling. Immediately afterwards, the cornea was lifted by its scleral lip and clamped between two Lucite chambers specially designed so as to prevent the cornea from slipping between their jaws and injuring the epithelium or endothelium. The area of cornea separating the two chambers was 1.5 cm.^{2} A removable Lucite plug fitted into each chamber and reduced its volume to approximately 0.5 ml.; these plugs were bored with a ring of inflow channels and a single outflow channel so that fluid could be circulated over both faces of the cornea. In Figure 1, separate motor-driven syringes were connected to the inflow channel of each plug through lengths of plastic tubing. In each tube was inserted a T-piece, the side arm of which held a silver-silver chloride electrode embedded in 3% agar. The outflow

Submitted for publication June 11, 1959.

This work was supported in part by a "Fight for Sight" award of the National Council to Combat Blindness, Incorporated, New York City.

An abstract of this work was presented at the New York Academy of Sciences on April 13, 1959; and at the Eastern Section meeting of the Association for Research in Ophthalmology on November 22, 1958.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons (Dr. Donn, Miss Mills) and the Institute of Ophthalmology, London, England (Dr. Maurice).

* The constituents are: sodium chloride (0.90%) 100 ml.; potassium chloride (1.15%) 5.0 ml.; calcium chloride (1.22%) 1.0 ml.; magnesium sulphate hepta hydrate (3.82%) 0.6 ml.; monobasic potassium phosphate (2.11%) 1.0 ml.; sodium bicarbonate (1.30%) 42.0 ml.; dextrose (12.0%) 1.00 ml.; total, 150.6 ml. A mixture of 5% carbon dioxide and 95% oxygen was bubbled through the solution until the pH was 7.38.

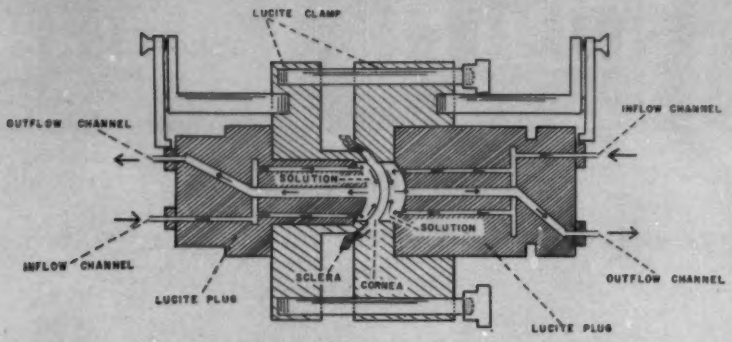


Fig. 1.—The cornea is clamped and the Lucite plugs are in position. Fluid circulates through the inflow channel into the space adjacent to each corneal surface and exits through the outflow channel.

from each chamber passed through 30 cm. lengths of polyethylene tubing 0.4 mm. in diameter, the ends of which dipped into beakers of saturated potassium chloride solution. The surface of the fluid in the beaker corresponding to the inside of the eye was placed 20 cm. above the other so that the cornea was inflated by its normal pressure. When samples were required the outflow was collected in small test tubes at the appropriate level. The plastic clamp containing the cornea was supported in an oil bath at 37 C. In some experiments the temperature of the oil bath was lowered to 4 C.

To measure the electric potential difference across the cornea each outflow tube was immersed in a beaker of potassium chloride, and these were connected by means of calomel electrodes to an electrometer (General Radio Company, Model 1230-A). This instrument measures to an accuracy of ± 0.5 mv. and has an input impedance of 10^{14} ohms.

The electric resistance of the cornea was estimated at intervals by passing a small direct current through it and a 10,000-ohm resistance in series and comparing the voltages developed across them. The current was passed through the cornea by way of the reversible electrodes inserted in the inflow tubes. The potentials were recorded with the DC electrometer; in the case of the cornea it was measured between the two beakers of potassium chloride solution, and the standing potential was subtracted from the recorded value. In Figure 2, the potential generated across the cornea was proportional to the current and reversible with it up to 150 mv.; it was kept to less than one-third of this value in practice.

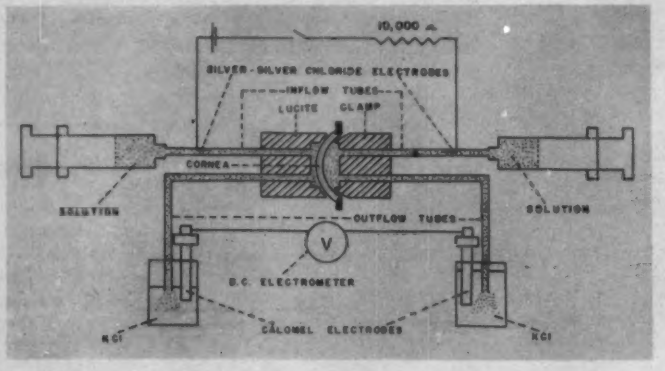


Fig. 2.—Schematic representation of the method of perfusing the cornea and making electric measurements. Potential difference is measured across the outflow tubes. A known current passes through the cornea via the inflow tubes and the change in potential is a measure of corneal resistance.

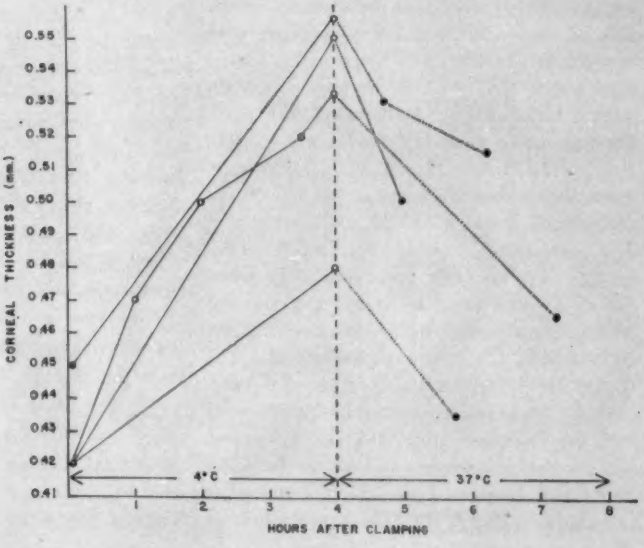
The ion flux was measured by adding approximately 1 mc. of essentially carrier-free Na^{24} to 50 ml. of solution in one of the syringes. Samples were taken from the outflow tubes on both sides of the cornea at intervals throughout an experiment. After appropriate dilution of the active solution, 0.5 ml. samples were dried on absorbent paper which had been previously glued to the bottom of a metal planchet, and the radioactivity was measured using a standard end-window counter (Nuclear Instrument and Chemical Corp., Model 3031-A).

In some experiments, the Lucite clamp was withdrawn from the oil bath and the plug adjacent to the epithelial surface was removed. The entire clamp was mounted on a slit lamp which had been fitted with a corneal pachometer (Sterrks Martin, Ltd.), as described by Maurice and Giardini,[2] and the thickness of the cornea at its center was measured by taking the average of six separate readings.

Results and Comment

Optical Measurements.—Optical measurements of corneal thickness revealed no significant difference between the cornea of a living rabbit and the same cornea mounted in the clamp 10 minutes later. If the dissection and clamping were sufficiently gentle, these corneae could maintain almost normal thickness for up to six hours. The Table shows the thickness of eight corneae before and after six hours at 37 C in the clamp, while Graph 1 shows the increase in thickness of four corneae similarly treated at 4 C. Furthermore, the clamped corneae having first swollen at 4 C were then able to lose thickness when warmed to 37 C (Graph 1).

Although the epithelium and endothelium must be somewhat traumatized by the dissecting and clamping procedure, it seems that enough viability remains in this preparation to allow the cornea to behave as it does in the undisturbed enucleated eye. The changes in the corneal thickness measurements at 37 C, and at 4 C, and the ability of these corneae to lose fluid after having been previously cooled agree well with the findings of Langham and Taylor[3] on enucleated eyes. This corresponds to the corneal changes demonstrated by other techniques by Davson,[4,5] Harris and Nordquist,[6] Schwartz, et al., and Smelser and Ozanics,[7] and shown by these workers to depend upon



Graph 1.—Changes in thickness of four corneae maintained at 4 C and then at 37 C.

Thickness of Corneae (in mm.)

Expt. No.	Immediately After Clamping	6 Hours After Clamping at 37 C
1	0.42	0.38
2	0.37	0.40
3	0.43	0.43
4	0.42	0.45
5	0.43	0.44
6	0.43	0.43
7	0.39	0.41
8	0.42	0.47
Av.	0.41	0.43

the metabolic activity of the epithelium or endothelium or both.

Electric Measurements. — The preparations differed considerably in electric resistance, and for a given preparation the resistance varied with time, usually increasing for the first hour and then remaining constant or slowly falling, Graphs 2 and 3. As can be seen from Graph 4, the range of peak resistance at 37 C was from 2,000 to 6,000 ohms. When the epithelium was scraped off, this resistance immediately fell to below 50 ohms, while if the endothelium was removed, no immediate change was noted.

Measurements of the electric potential across the corneal preparation in over 100 experiments showed that the aqueous humor side of the cornea was always positive with respect to the tear fluid side. Generally, it took one to two hours to develop maximum values, which it then maintained with small fluctuations or slow fall-off for six to eight hours (see Graphs 2 and 3). The scattergram shows that the range of peak potential differences reached in 20 experiments at 37 C was from 15 to 42 mv. This potential disappeared instantly and completely when the epithelium was removed, but no immediate change was noted on removing the endothelium. In four experiments at 3-4 C the potential difference never exceeded 3 mv.

In each corneal preparation the potential and the resistance rise and fall in phase; and for the experiments as a whole there is a correlation between peak voltages and peak resistances (Graph 4). This association is probably accounted for by the fact that the available potential generated by the epithelial metabolism is shorted out by a lowering of resistance.

The resistance of the epithelium both to electric current and to the flux of ions is about 25,000 times greater than a layer of aqueous humor of equal thickness. This emphasizes the importance of using the utmost care in preparation of the tissue, as the slightest epithelial damage can cause a large drop in resistance. This probably accounts for the low values of resistance found by Holt and Cogan,[8] and the low potential reported by Potts and Modrell.[9] Since these workers used beef corneae, it is possible that this discrepancy could be the result of species differences, but it is most probably the result of slight trauma in the dissection and mounting of the tissue. In 1957, Babbott,[10] measured the impedance of beef corneae, area not given, and reported an average reading of 1,200 ohms at 1,000 cps with a capacitive phase angle of 27 degrees.

Sodium Flux Measurements.—The permeability coefficient for the isolated cornea can be calculated from the activity of radioactive sodium in the fluid collected from the two chambers of the system. Once a steady state has been established, the rate at which Na^{24} is collected on the inert side must equal the flux of the ion across the cornea from the active side. Calling a_o the activity of Na^{24} in the active perfusate, and a_s the steady state activity which is developed in the inert perfusate, the flux of radioactive sodium across the cornea is given by $KA(a_o-a_s)$, where K is the permeability coefficient, and A the exposed area of the cornea. Since a_o is some 4,000 times greater than a_s, this expression may be written $KA\,a_o$.

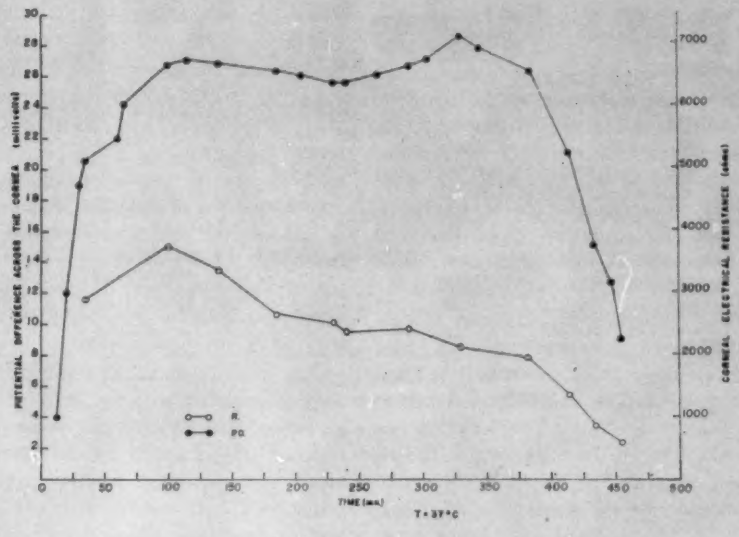
The rate at which Na^{24} is collected from the inert chamber is given by va_s, where v is the rate of flow.

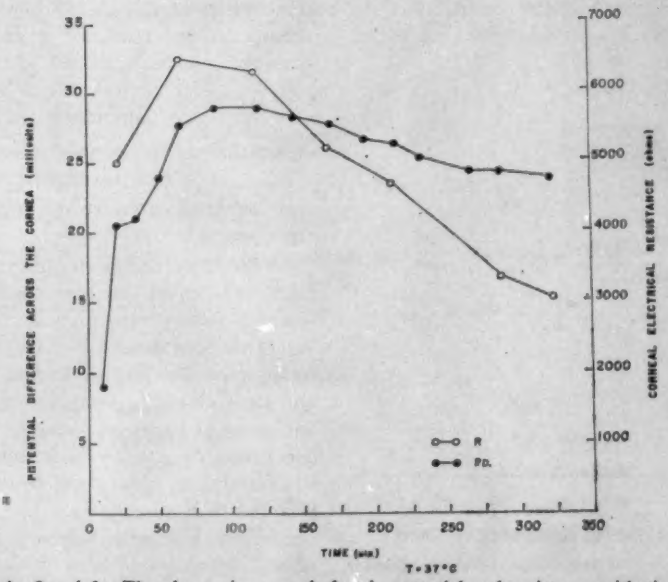
Therefore at the steady state

$$va_s = KA\,a_o \text{ or } K = \frac{va_s}{Aa_o}$$

The total flux of sodium across the cornea will be given by $KACa$, where C_o is the total sodium concentration, 0.145 moles per liter.

It can readily be shown that if mixing within the chamber is efficient the steady state will be approximated according to the exponential of $\frac{vt}{V}$, where t is the time and V the volume of the chamber. Since V is 0.5 ml. and v is 5 ml. per hour, this implies that the concentration of Na^{24} in the perfusate should be within 1% of its steady



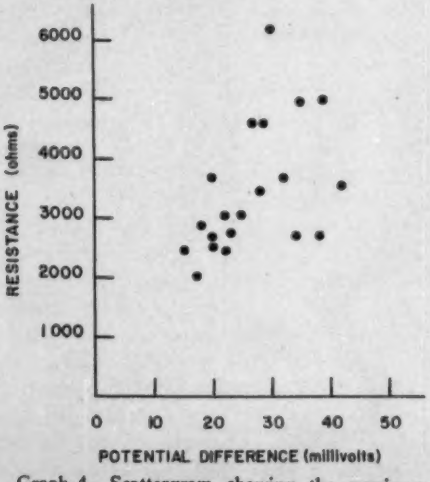


Graphs 2 and 3.—The change in corneal electric potential and resistance with time in two experiments.

state value within 30 minutes. This appeared in practice to be the case.

It will be shown in a subsequent paper that the values of K obtained in this way are dependent both on the value of the potential across the cornea and on the direction in which the flux is being measured. For our present purpose, to establish a rough estimate of the resistance of the tissue to ionic diffusion, no correction was made for the potential, and the values of the permeability measured in the two directions were sufficiently close for them to be combined. The values of K found in 20 corneae then fell between the limits 0.0008 and 0.0028 cm. per hour.

In these experiments Na must diffuse across the entire corneal thickness in order to reach the opposite chamber, but the combined stromal and endothelial resistance to the passage of Na is sufficiently low compared to that of the epithelium to be disregarded. Maurice [11,12] found that the combined stroma and endothelium in the living rabbit was approximately 70 times more permeable to Na than the epithelium, and the values of electric resistance found in the present experiments confirm this difference in ionic permeability. Thus the coefficient of permeability which is established in these experiments is a measure of the permeability of the corneal epithelium alone.



Graph 4.—Scattergram showing the maximum corneal potential difference and electric resistance in 20 experiments at 37 C.

Maurice originally found the epithelial coefficient of permeability for Na in living rabbits to be in the range of 0.0008-0.0024 cm. per hour. Several years [13] later he found that 50 of 54 determinations were in the range of 0.0003-0.0009 cm. per hour, and was unable to explain this lack of consistency. The range of values in the present experiments correspond to the earlier in vivo series and overlap the later ones. If it is considered that a dehiscence in the epithelium of 1% of the surface area will about double the corneal permeability, the agreement between the values in vitro and in vivo is quite satisfactory.

The description above is of corneae that were considered to have been successfully prepared. A significant proportion (approximately 10%) evinced a small electric resistance and potential after clamping and sometimes were unable to maintain their normal thickness. These tissues had clearly been damaged during their preparation; on most occasions the operator was aware of some mishandling that could account for the trauma. A few remained in which the failure could not be explained.

Summary

A technique is described whereby a rabbit cornea can be clamped in vitro between two chambers and kept alive and functioning for eight hours.

Under these conditions the cornea maintains the ability to lose thickness when warmed after previous cooling; its electric resistance is of the order of several thousand ohms, virtually all due to the epithelium; and the epithelium generates an electric potential up to 40 mv, the aqueous humor side being always positive with respect to the tear fluid side. The coefficient of permeability of these preparations for $^{*}Na^{24}$ agrees reasonably well with values previously reported in living rabbits.

630 W. 168th St. (32).

REFERENCES

1. Schwartz, B.; Danes, B., and Leinfelder, P. J.: The Role of Metabolism in the Hydration of the Isolated Lens and Cornea, Am. J. Ophth. 38:182 (July, Pt. 2) 1954.

2. Maurice, D. M., and Giardini, A. A.: The Corneal Thickness, and the Average Thickness of the Human Cornea, Brit. J. Ophth. 35:169 (March) 1951.

3. Langham, M. E., and Taylor, I. S.: Factors Affecting the Hydration of the Cornea in the Excised Eye and the Living Animal, Brit. J. Ophth. 40:321 (June) 1956.

4. Davson, H.: Hydration of the Cornea, J. Physiol. 125:15P (May) 1954.

5. Davson, H.: Hydration of the Cornea, Biochem. J. 59:24 (Jan.) 1955.

6. Harris, J. E., and Nordquist, L. T.: The Hydration of the Cornea: I. The Transport of Water from the Cornea, Am. J. Ophth. 40:100 (Nov., Pt. 2) 1955.

7. Smelser, G. K., and Ozanics, V.: Structural Changes in Corneas of Guinea Pigs After Wearing Contact Lenses, A.M.A. Arch. Ophth. 49:335 (March) 1953.

8. Holt, M., and Cogan, D. G.: The Cornea: VIII. Permeability of the Excised Cornea to Ions, as Determined by Measurements of Impedance, Arch. Ophth. 35:292 (March) 1946.

9. Potts, A. M., and Modrell, R. W.: The Transcorneal Potential, Am. J. Ophth. 44:284 (Nov., Pt. 2) 1957.

10. Babbott, E.: The Effect of Certain Drugs of Corneal Impedance, A.M.A. Arch. Ophth. 57: 425 (March) 1957.

11. Maurice, D. M.: The Permeability to Sodium Ions of the Living Rabbit's Cornea, J. Physiol. 112:367 (Feb.) 1951.

12. Maurice, D. M.: The Permeability of the Cornea, Ophth. Lit. 7:3 (June) 1953.

13. Maurice, D. M.: Influence on Corneal Permeability of Bathing Solutions of Differing Reactions and Tonicity, Brit. J. Ophth. 39:463, 1955.

Studies on the Living Cornea In Vitro

II. The Active Transport of Sodium Across the Epithelium

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It is generally believed that the normal corneal stroma has a tendency to swell in vivo and that this tendency is countered by some metabolic process in the epithelium, or endothelium, or both.[1-10] One way that this process could act is through the removal of one or more of the constituents of the tissue fluid of the stroma across the cellular surface layers of the cornea. The active transport of water or of any single solute present to the extent of 5 millimoles per liter could be effective in overcoming the swelling force of the stroma.[11] Harris [12,13] has presented some evidence that water itself is actively moved, but others [1,11,14] have suggested that the active transport out of the stroma of an ion such as Na might be a more efficient mechanism.

The isolated corneal preparation described in the previous paper has been used to study the active transport of Na in the epithelium.

Methods

Rabbit corneae were excised and clamped between two Lucite chambers as described in the previous paper. The resistance of the preparation was measured every 20 minutes. In some experiments the electric potential developed by the cornea was noted at the same time. In others, a known current was passed through the cornea by way of the inflow tubes so as to maintain the potential as measured across the outflow tubes at zero value, the technique first described by Ussing.[15]

In a preliminary group of experiments, the flux of Na was measured in one direction only across the cornea during an experiment. The Na was labeled with radio-Na^{24}, and the total Na flux was determined by the ratio of the activities of the efflux from the two chambers and the perfusion rate, as described in the previous paper.

In the second group, the flux was measured successively inwards and outwards across one cornea in each experiment. After a steady state had been established in the first direction for a few hours, the perfusing syringes were switched and the experiment continued. In order to hasten the establishment of the second steady state, the plugs were removed and the chambers flushed out with the appropriate solution before the switch over. It was necessary always to measure the inwards flux first, because when the inner surface of the cornea was in contact with the active solution the stroma acquired a very great activity which could not be washed out within the useful life of the preparation.

In the final group of experiments, Na fluxes were measured in both directions simultaneously by separately labeling the two perfusing solutions with the radioactive isotopes, Na^{24} and Na^{22}. The use of an Al. filter 0.3 mm. in thickness over a dried sample reduced the measured activity of Na^{22}

Submitted for publication June 11, 1959.

This work was supported in part by a "Fight for Sight" award of the National Council to Combat Blindness, Incorporated, New York City.

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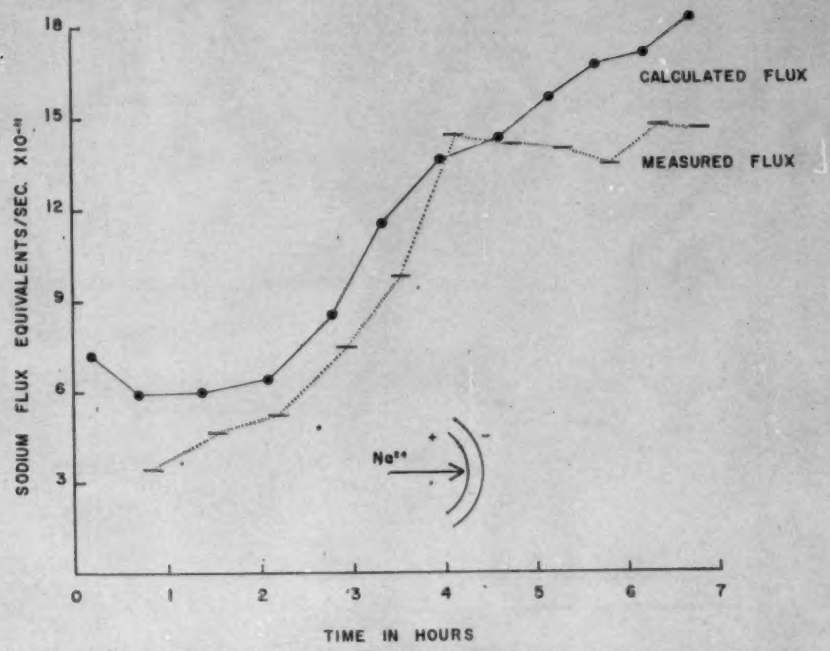


Fig. 1.—Measured and calculated outflux of sodium across the cornea during a seven hour period.

by approximately 92% and that of Na^{24} by only 50%, thus allowing small amounts of Na^{24} to be counted in the presence of Na^{22}. Counts were repeated three weeks later with the same filter in place, by which time all Na^{24} had disappeared; and the difference between the three week count and the count made on the day of the experiment was a measure of Na^{24} activity. Na^{22} fluxes were measured simply by recounting all samples without the filter three weeks after the experiment.

Results

One test for active transport used in this paper is to measure the flux of Na across the cornea in the two directions, and to compare the ratio of the values with the ratio that would be expected if the cornea presented an inert resistance to the movement of the ion. A difference between the experimental and theoretical values implies that the cornea is playing an active part in the movement of the ion; this is particularly significant if the Na flux is found to be greater in the direction which raises its electrochemical potential energy.

In these experiments the concentration of Na and therefore the chemical activity on the two sides of the cornea was always equal. Then the flux of Na in the two directions across the exposed surface of the cornea S_{in} and S_{out} will be given by:

$$S_{in} = \frac{G'inE}{\left(e^{\frac{EF}{RT}} - 1\right)_F} \qquad (1)$$

$$S_{out} = \frac{G'outEe^{\frac{EF}{RT}}}{\left(e^{\frac{EF}{RT}} - 1\right)_F} \qquad (2)$$

if the cornea is acting as an inert membrane.[16] The area of exposed corneal surface in all experiments is 1.5 cm.^{2} and flux is expressed as equivalents per second for the exposed cornea. G' is the partial conductance of the cornea towards Na, in *mhos*; E is the electric potential across it, the inside positive; and R, T, and F are, respectively, the

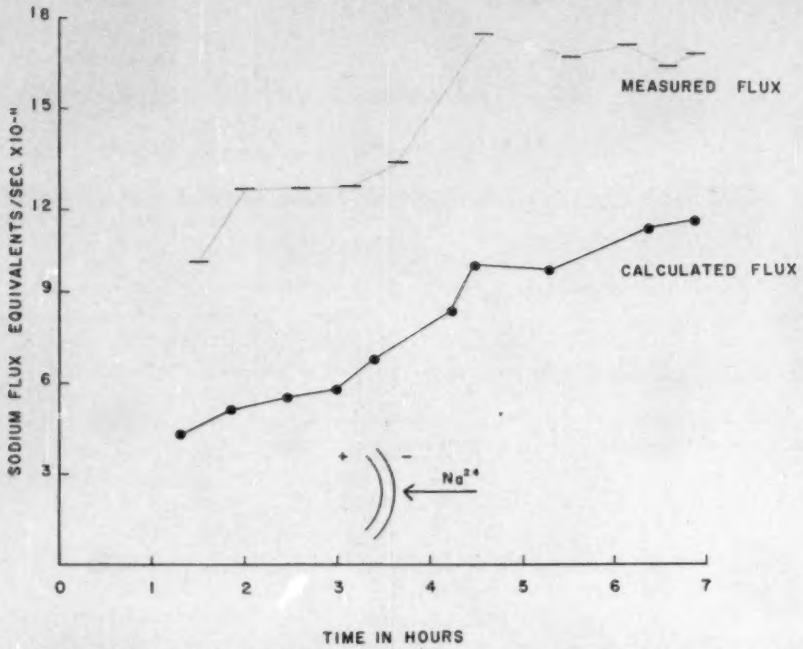


Fig. 2.—Measured and calculated influx of sodium across the cornea during a seven hour period.

gas constant (8.3 joules per mole per degree), the temperature, and Faraday's constant (96,500 coulombs per mole). At any given moment G'_{in} and G'_{out} will be equal to one another, but the equations are written in this form because in some of the experiments the influx and outflux were measured at separate times between which the conductances might have changed. In an inert membrane the partial Na conductance may be assumed to be proportional to the total conductance so that

$$\frac{G'_{in}}{G_{in}} = \frac{G'_{out}}{G_{out}} = p \qquad (3)$$

when G_{in} and G_{out} are the electrically measured conductances of the exposed cornea.

In order to compare the experimental values of the influx and outflux when they are not determined simultaneously, it is convenient to assume a suitable value of p, and calculate the theoretical values of S_{in} and S_{out} from equations 1, 2, and 3, employing the measured electrical properties of the cornea. The experimental and theoretical fluxes can then be plotted on a graph and it can be seen at a glance whether their ratio is the same for each direction of movement. The value one-half was arbitrarily given to p. Although this value is not necessarily correct, it would introduce the same proportional error for fluxes calculated in each direction. Thus, even though the theoretical fluxes may not be accurate, the ratio of measured fluxes to calculated fluxes should be the same in each direction if no active transport takes place.

In the first experiments, the flux was measured in one direction only and the potential across the cornea was allowed to develop without interference. The measured Na^{24} flux in general varied in conformity to that calculated by equations 1 and 2. (Graphs 1 and 2.) In eight experiments the measured influx had a mean of 1.26 times the calculated value (±10%) and in seven experiments the outflux had a mean of only

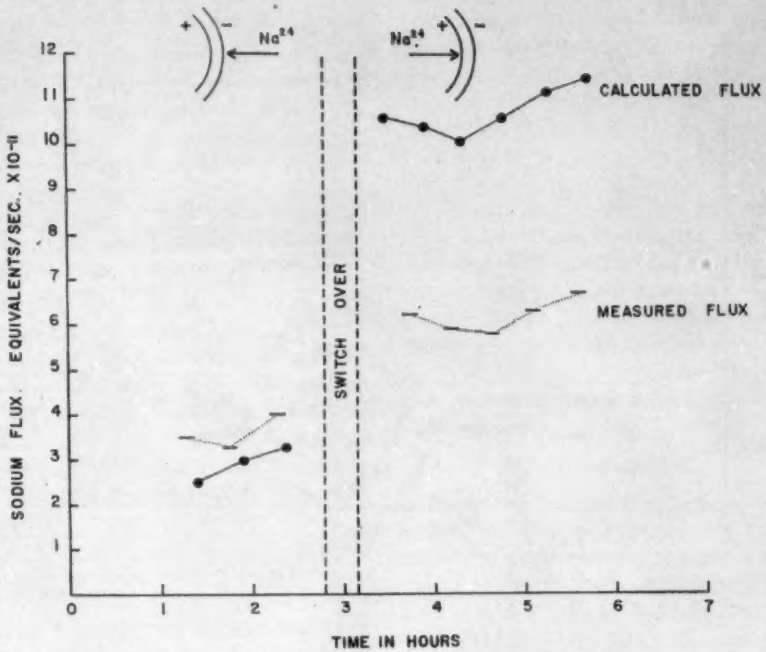


Fig. 3.—Consecutively measured flux of sodium in both directions across the same cornea; corneal potential not neutralized.

0.65 times (±10%). This suggested therefore that the cornea was not behaving as an inert membrane.

In the second series, the flux was measured in both directions across one cornea. In some cases the voltage across the cornea was allowed to develop freely (Graph 3) and in others it was reduced to zero by means of an external current (Graphs 4 and 5); in the latter condition

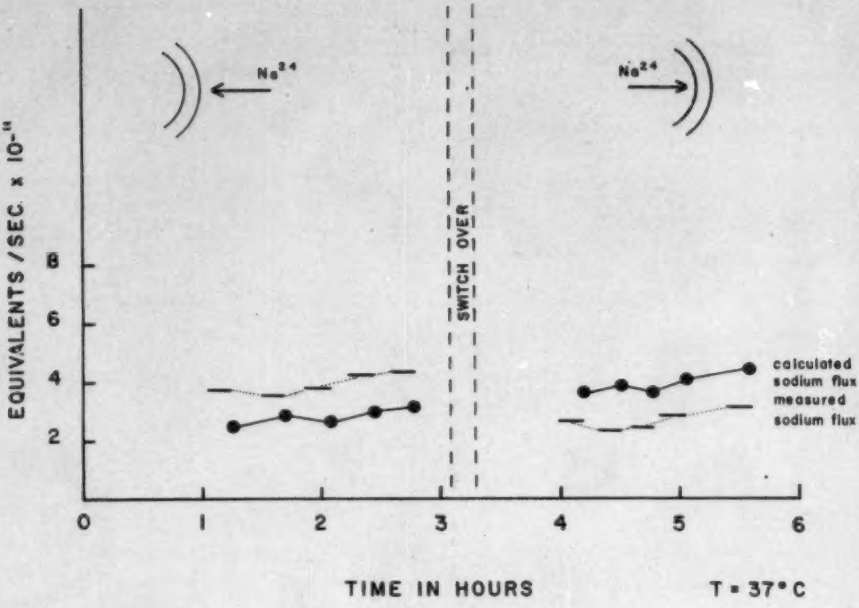
$$S_{in}=S_{out}=\frac{G'RT}{F^2} \qquad (4)$$

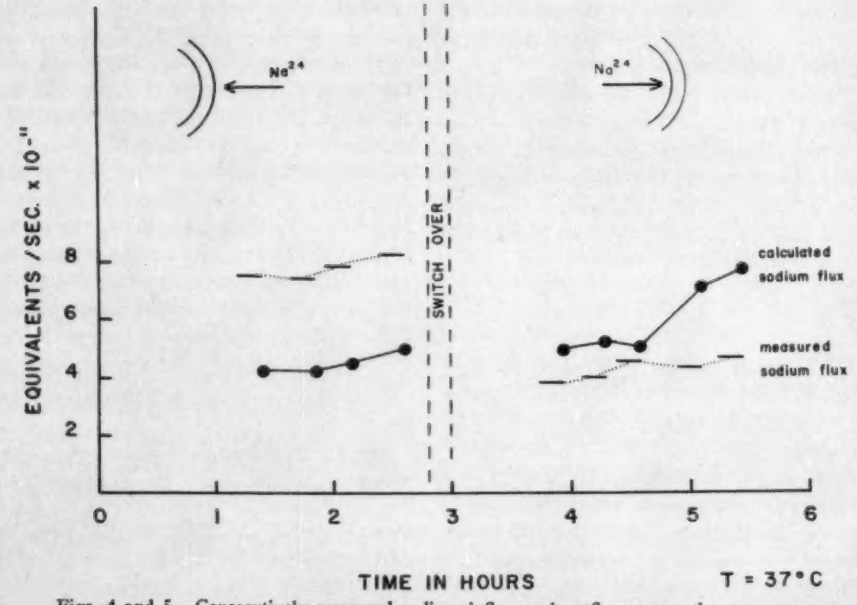
for an inert membrane.

In every case the inward flux is relatively greater than the outward flux compared to the calculated values, indicating an inwards transport of Na even against the electric potential gradient.

In Table 1 are summarized the detailed results of the experiments in which the voltage was zero. A numerical comparison is made of the measured influx and outflux. The total conductance of the cornea generally rises during an experiment, and to make a comparison the outflux is corrected to the value it would have had during the influx measurements if the conductance had remained constant, using equations 3 and 4. It is seen that the influx is in most cases about double the corrected outflux, confirming an inwards active transport of Na. The difference between the influx and outflux, Column G, shows the current carried across the cornea by the transported Na ions. The total current passing across the cornea at this time is given by the neutralizing current, Column H; the Na ion current represents a major fraction of the total.

Column I shows the partial conductance of the cornea to Na in the outward direction as calculated by equation 4 compared to the total corneal conductance. On the assumption that the cornea is inert as far as the outflux of Na is concerned this fraction is p, the ration of the Na conductance





Figs. 4 and 5.—Consecutively measured sodium influx and outflux across the same cornea; corneal potential neutralized.

to the total conductance as defined in equation 3; the values lie between 0.33 and 0.50.

Four experiments were performed at a temperature of 3 to 4 C; in these the cornea developed no voltage greater than 3 mv. The results show (Graph 6) that both the measured influx and outflux bear approximately the same relationship to the calculated flux. There is then no evidence of an active transport of Na at this temperature. The average value of p in these experiments was 0.35.

In the final experimental series, the Na flux was measured in both directions simultaneously across the cornea with the potential reduced to zero. There is no need to assume that p in equation 3 remains constant with time in this case; the influx and outflux can be compared directly. The results of seven experiments are shown in Table 2. It can be seen that the influx is on the average more than twice the simultaneously measured outflux. A comparison of the neutralizing current and the net flux in the adjoining columns shows that their ratio is 1.24; if experiment Number 2 is excluded, however, the ratio of neutralizing current to net Na flux is a little greater than unity, 1.09. It is not improbable, therefore, that the Na ion carries most if not all the current. Graph 7 shows the simultaneous fluxes and neutralizing current in a single experiment and illustrates how the net flux keeps pace with the neutralizing current. The average value of p for the outward movement of Na in these experiments is 0.32.

In each determination of Na flux sources of error appeared in pipetting 0.5 ml. samples into the planchets, in measuring radioactivity, usually at least 2,000 counts for each determination, and in variations in the perfusion rate of less than 2%. In addition, there appeared to be occasional irregularities of mixing in the chambers adjacent to the cornea; this sometimes caused isolated large variations in measured flux, but over a period of time this evened out (see Graph 1). It is estimated that the over-all error in individual flux measurements is less than $\pm 10\%$. The neutralizing current was measured with an accuracy of better than $\pm 2\%$, but sometimes it was found on checking each 5 minutes that the cornea's potential was over or under neutralized by 2 mv. When this occurred it was immediately corrected. In the switch-over experiments there is the additional error due to the mild trauma in removing the Lucite plugs and the possibility that slight slippage occurs, thus exposing a slightly different area of cornea for the outflux measurements. Finally, it should be remembered that for each separate cornea there is a great variability in the trauma of dissection and clamping.

Comment

These experiments show that the isolated cornea can develop a net flux of Na even against an electrochemical gradient; the Na must be actively transported by the cornea as a result of its metabolism. This movement of Na is roughly equivalent to the current passing through the cornea when the potential difference across it is zero. Although the equivalence is not exact, it suggests that it might be the only active movement of charged particles; it does not rule out, however, the active transport of further ions across the cornea in such a way that the electrical balance is maintained.

An unexpected finding is that the direction of the active transport of Na across the epithelium is into the corneal stroma, rather than out of it, as had been suggested by some. The magnitude of the net flux, 7.6×10^{-11} eq per sec in the case of the double tracer experiments, corresponds to 6.5×10^{-9} eq per min for the whole cornea 2.1 cm.^{2} in area. This is close to the active *outward* transport estimated to be necessary to maintain the correct thickness, 7.5×10^{-9} eq per min, on the basis of the Na permeability and swelling pressure of the cornea.[11] However, the experimental results cannot be explained by assuming that the endothelium actively transports Na out of the stroma into the aqueous humor and

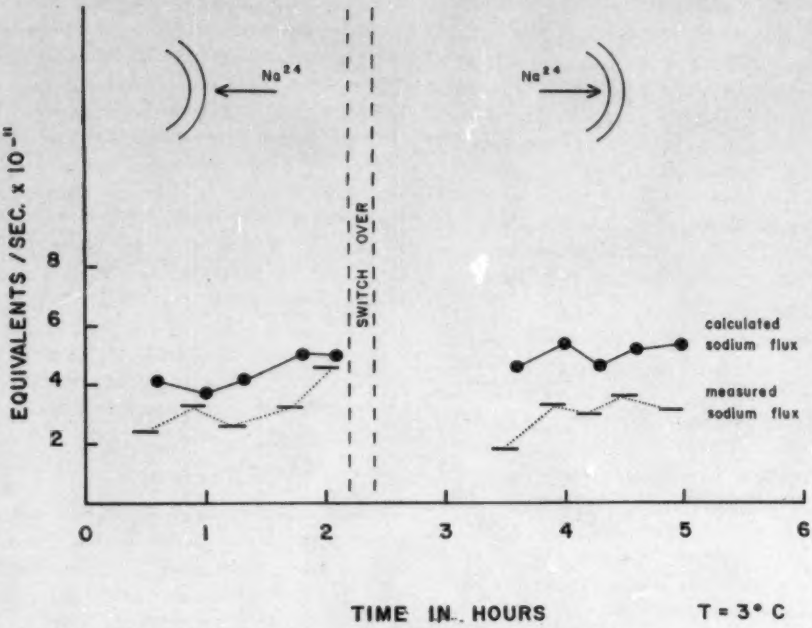


Fig. 6.—Consecutively measured sodium influx and outflux across the same cornea at 3 C.

that the measured movement across the epithelium follows passively. The influx of Na across the epithelium is about double the outflux. If this were a passive movement, the electrochemical activity of the Na ions in the stroma would be half of that in the solution bathing the epithelium. It would be expected therefore that the Na concentration in the stroma would be about half that elsewhere, or that the endothelium would be capable of maintaining the stroma about 18 mv. negative with respect to the epithelial solution, or some compromise between the two. In fact, the Na concentration within the stroma is found to be greater than in body fluids in accordance with a Donnan equilibrium,[17] and after scraping away the epithelium the potential across the endothelium is found to be negligible. Another argument against this possibility is that it requires more energy than that available from the total metabolism of the endothelium. Not only would there be a passive movement of Na across the epithelium, but also one a hundred times greater into the stroma across the endothelium; this also would have to be actively removed. A calculation of the energy required to move this up the large potential gradient shows that it is of the same order as that provided by the metabolism of the whole cornea of which the endothelium shares only a very small fraction (Langham, 1954).

The present finding of a relatively large inward active transport of Na conflicts with experiments in vivo in which it was reported that the inward flux of labeled Na was independent of the reaction of the bathing solution in the range of pH 4-10 and was proportional to the concentration of the Na ions in the solution in the range 0.1% to 3% NaCl.[18] A fall in the influx to one-half of its normal value as the result of the suppression of active transport should have been detected in those experiments. One difference between the two sets of experiments is that in the earlier ones the bathing fluid was only in contact with the epithelium for 10 minutes instead of

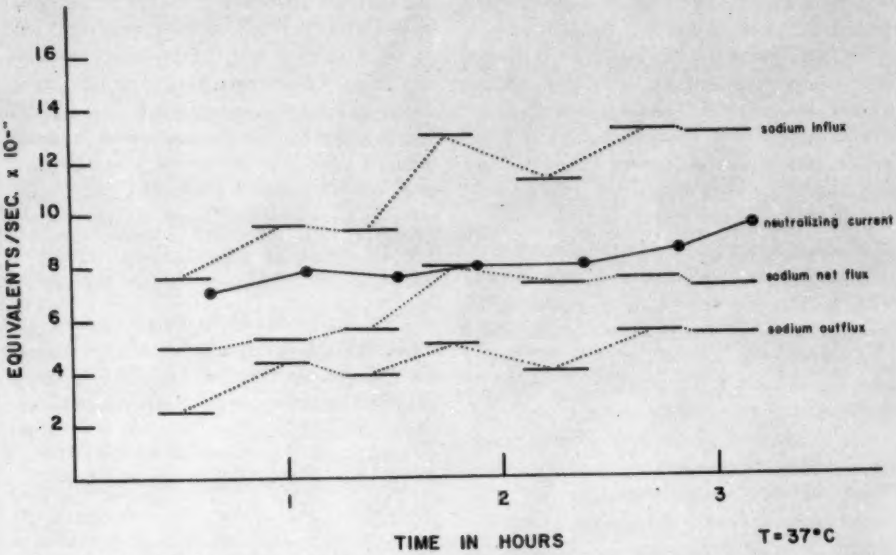


Fig. 7.—Simultaneous values of influx, outflux, and neutralizing current when the corneal electric potential was neutralized. The net flux follows the same course as the current.

several hours. It is possible that this was not sufficient time for the changes to take effect.

The active transport of Na across the epithelium produces a positive potential on the stromal side of the epithelium which in the absence of a neutralizing current tends to drive the Na outwards across the epithelium. If the epithelium were impermeable to anions, this potential would build up to a value sufficient to cause a passive outflux equal to the active influx. It appears from the present experiments that the Na partial conductance under is one-half the total conductance of the epithelium, and it is therefore probable that the permeability of the epithelium towards anions is similar in magnitude to that towards Na. The positive potential will then maintain a value which draws anions inwards across the epithelium at a rate equivalent to about one-half of the active flux and drives out a similar quantity of Na ions so as to retain the electrical balance. As a result there

TABLE 1.—*A Comparison of Na Flux Measurements and Neutralizing Current Across the Rabbit Corneal Epithelium* When the Potential Was Zero*

A	B	C	D	E	F	G	H	I
Expt.	Measured Na Influx**	Conductance During B M. Mhos	Measured Na Outflux**	Conductance During D M. Mhos	Corrected Na Outflux During B $\frac{C}{(D \times E)}$**	Net Na Flux (B-F)**	Neutralizing Current During B**	p During Outflux Measurements
1	4.0	0.20	2.5	0.27	1.9	2.1	3.2	0.33
2	7.7	0.32	4.1	0.37	3.5	4.2	5.0	0.40
3	6.6	0.37	6.2	0.51	4.5	2.1	5.2	0.44
4	7.3	0.31	7.8	0.57	4.2	3.1	5.9	0.49
5	8.2	0.28	6.2	0.45	3.9	4.3	3.5	0.50
Av.	6.8	0.30	5.4	0.43	3.6	3.2	4.6	0.43

* Area of exposed corneal surface=1.5 cm^2.
** Equivalents per second×10^{-11}/cornea.

will be a movement of salt into the stroma equivalent to about one-half the active transport flux. Some of the salt that is moved into the stroma diffuses into the aqueous humor, but a steady state concentration develops which will tend to bring in some water and cause the cornea to swell over and above any swelling caused by the swelling pressure of the cornea itself.

It would appear then that the active transport of Na into the corneal stroma should tend to increase the swelling tendency of the cornea rather than to counter it. However, when the excised cornea is cooled and the inward Na transport is abolished the cornea swells, whereas when Na is actively transported the excised cornea maintains almost normal thickness for six hours. There are two possible solutions for this paradoxical finding. The more probable is that the active transport of Na into the stroma is not the essential metabolic mechanism which maintains normal corneal thickness; it could be an associated process or possibly is an independent one. There are many other processes that could maintain corneal thickness and are within the metabolic capabilities of the cornea. Water could be transported out across the limiting layers; uncharged salt molecules could be transported across either limiting layer; pinocytosis could transport both salt and water across either layer, or ions could be actively transported out across the endothelium. On the other hand, as Davson suggested, the corneal colloids may not tend to swell in vivo and the postmortem swelling might be secondary to metabolic interference. If this were the case, there would be no need to postulate an active outward transport process. The active inwards transport of Na might be related to the maintenance of the normal state of the corneal colloids.

TABLE 2.—*A Comparison of Simultaneously Measured Na Influx and Outflux Across the Rabbit Corneal Epithelium* When the Potential was Zero*

Expt. No.	Influx**	Outflux**	Net Flux**	I**	I / Net Flux
1	12.50	5.10	7.40	8.6	1.16
2	10.11	5.40	4.71	10.15	2.16
3	6.68	1.31	5.37	6.55	1.22
4	10.95	1.84	9.11	7.36	.74
5	14.10	6.73	7.37	7.88	1.07
6	14.68	8.56	6.12	7.46	1.22
7	14.05	3.94	10.1	12.02	1.09
Av.	11.87	4.70	7.17	8.57	1.24

* Area of exposed corneal surface=1.5 cm².
** Equivalents per second×10⁻¹¹/cornea.

Summary

The measured Na^{24} fluxes across the rabbit corneal epithelium are compared with the theoretical flux values, derived from electrical measurements, which would be obtained if the epithelium behaved as an inert membrane.

The influx and outflux of Na across the epithelium are measured simultaneously while the epithelial potential is neutralized.

Both experiments demonstrate that Na is actively transported across the epithelium into the corneal stroma and that the net flux of Na is equivalent to most of the neutralizing current.

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REFERENCES

1. Davson, H.: Hydration of the Cornea, J. Physiol. 125:15P (May) 1954.

2. Davson, H.: Hydration of the Cornea, Biochem. J. 59:24 (Jan.) 1955.

3. Harris, J. E., and Gruber, L.: The Hydration of the Cornea: III. The Influence of the Epithelium, Am. J. Ophth. 42:330 (Oct., Pt. 2) 1956.

4. Langham, M. E.: Relation of Corneal Respiration to Hydration and Opacification, XVII Conc. Ophth. Acta 1:500, 1954.

5. Langham, M. E.: The Effect of Aerobic Metabolism on the Movement of Water and Sodium in the Rabbit Cornea, J. Physiol. 128:43P (March) 1955.

6. Langham, M. E., and Taylor, I. S.: Factors Affecting the Hydration of the Cornea in the Excised Eye and the Living Animal, Brit. J. Ophth. 40:321 (June) 1956.

7. Schwartz, B.; Danes, B., and Leinfelder, P. J.: The Role of Metabolism in the Hydration of the Isolated Lens and Cornea, Am. J. Ophth. 38:182 (July) 1954.

8. Smelser, G. K.: Relation of Factors Involved in Maintenance of Optical Properties of Cornea to Contact Lens Wear, A.M.A. Arch. Ophth. 47:328 (March) 1952.

9. Smelser, G. K., and Chen, D. K.: A Comparative Study of the Structure and Hydration Properties of Corneas Adapted to Air and Aquatic Environments, XVII Conc. Ophth. Acta 1: 490, 1954.

10. Smelser, G. K., and Ozanics, V.: Structural Changes in Corneas of Guinea Pigs After Wearing Contact Lenses, A.M.A. Arch. Ophth. 49:355 (March) 1953.

11. Maurice, D. M.: The Permeability to Sodium Ions of the Living Rabbit's Cornea, J. Physiol. 112:367 (Feb.) 1951.

12. Harris, J. E.: The Physiologic Control of Corneal Hydration, Am. J. Ophth. 44:262 (Nov., Pt. 2) 1957.

13. Harris, J. E., and Nordquist, L. T.: The Hydration of the Cornea: I. The Transport of Water from the Cornea, Am. J. Ophth. 40:100 (Nov., Pt. 2) 1955.

14. Potts, A. M.: The Nutritional Supply of Corneal Regions in Experimental Animals: II. The Problem of Corneal Transparency and the Tonicity of Tears, Am. J. Ophth. 36:127 (June, Pt. 2) 1953.

15. Ussing, H. H.: The Active Ion Transport Through the Isolated Frog Skin in the Light of Tracer Studies, Acta physiol. scandinav. 17:1, 1949.

16. Linderholm, H.: Active Transport of Ions Through Frog Skin with Special Reference to the Action of Certain Diuretics, Acta physiol. scandinav. 27:1 (Supp. 97) 1952.

17. Davson, H.: Some Considerations on the Salt Content of Fresh and Old Ox Corneae, Brit. J. Ophth. 33:175 (March) 1949.

18. Maurice, D. M.: Influence on Corneal Permeability of Bathing Solutions of Differing Reactions and Tonicity, Brit. J. Ophth. 39:463, 1955.

Corneal Allescheriosis

A Case of Keratomycosis Treated Successfully with Nystatin and Amphotericin B

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The purpose of this paper is to report a case of corneal ulcer with hypopyon and iridocyclitis, in which a mold identified as Allescheria boydii was demonstrated in scrapings from the eye in situ and imminent perforation averted by appropriate therapy. This appears to be the second recorded case of corneal ulcer associated with A. boydii (Monosporium apiospermum)[1] and the first to be successfully treated.

A. boydii is a soil saprophyte which generally enters the human body by traumatic inoculation. When found in pathological situations it is most frequently implicated as an etiological agent of "madura foot." However, it has also been incriminated in such diverse conditions as meningitis,[2] fatal pulmonary infection,[3] and mycetoma of the eyelid.[4] Exhaustive reviews of the literature on A. boydii and M. apiospermum infections have been published in recent years,[5,6] as has a study on the biology of these organisms.[7]

Isolated involvement of the eyeball has been reported a number of times in association with a variety of fungi,[8] but in most cases no cultures were obtained, identification being based upon nonspecific fungal structures in the tissues. In other instances, no organisms were seen upon direct examination but pathology was attributed to some saprophyte subsequently obtained in culture. Valid assignation of etiology has most often incriminated either Candida albicans or Aspergillus fumigatus. Recently a case of keratoconjuctivitis ascribed to C. albicans was successfully treated with nystatin,[9] and experimental moniliasis in rabbits was found to respond both to nystatin and to amphotericin B.[10] A number of cases of corneal ulcer attributed to C. mycoderma have been seen in Argentina during the past five years.[11] These have reportedly been cured by repeated scraping of the ulcer, followed by topical trichloracetic acid or iodine tincture.

In 1955, Pautler et al.[1] reported a case of mycotic corneal ulcer and hypopyon in which the diagnosis was established after enucleation. Hyphae and spores were seen in exudate from the anterior chamber, and the organism was subsequently identified in culture as M. apiospermum. In the present case, after the demonstration of numerous conidia of M. apiospermum in KOH mounts of corneal scrapings, the eye was saved by appropriate antifungal therapy.

Clinical History

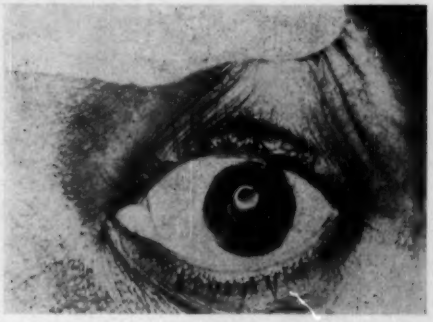
A 27-year-old Negro male fish-factory worker was admitted to the Roper Hospital on Sept. 3, 1958, with a complaint of pain, photophobia and lacrimation, and almost complete loss of sight in the left eye. He stated that, while working at the factory on Aug. 10th, 1958, he had been struck in the left eye by a fish scale. The patient had had neither previous difficulty in vision nor past trauma to either eye. Past history, family history, habits, and environment were noncontributory. Examination revealed a vision of 20/20 O. D.; light projection O. S. The left eye showed moderate swelling of the lids and a central corneal ulceration with deep infiltration in the corneal substance at the edge of the

Submitted for publication April 24, 1959.

ulcer. The examination showed numerous cells and a heavy aqueous flare in the anterior chamber. The iris was contracted and muddy. The fundus could not be observed. The remainder of the physical examination was within normal limits. Laboratory work showed normal blood picture and urinalysis. A specimen for culture was taken from the eye and submitted to the laboratory for bacterial studies, and immediate therapy was begun with Combiotic (penicillin and streptomycin, Pfizer), oral and topical chloramphenicol (Chloromycetin), sulfisoxazole (Gantrisin), and atropine locally. The next day hypopyon was forming and the globe appeared deeply injected; treatment with Neo-Delta-Cortef (a preparation of hydrocortisone and neomycin sulfate) was begun because of the intense reaction in the eye. On the third hospital day the corneal ulceration had abscessed. Neo-Delta-Cortef was discontinued on the sixth hospital day, and nitrofurazone (Furacin) ophthalmic solution was administered. At this time, the cornea began to thin and perforation appeared imminent (Fig. 1). An emergency corneal transplant was considered. Scrapings of the ulcer were taken specifically for mycological studies, and immediate direct examination of this material in a KOH mount revealed fungus hyphae and spores. Thereupon all drugs except atropine were discontinued and nystatin therapy (Mycostatin, Squibb) instituted as follows: 250 mg. orally every six hours; nystatin (Mycostatin crystalline, "for laboratory use only") in a suspension of 25,000 units per cubic centimeter of isotonic saline applied topically, one drop every 15 minutes during the day and every two hours at night. On the 10th hospital day the supply of topical nystatin was exhausted and the application of chloramphenicol ophthalmic ointment begun and continued for four days. During this time the eye appeared to get worse. On the 11th day, application of amphotericin B (Fungizone for infusion, Squibb) was begun, one drop of a suspension of 0.1 mg. per cubic centimeter in distilled water in the affected eye every 30 minutes. Nystatin drops were resumed on the following day in the same concentration as previously given, every 15 minutes together with amphotericin B. On the 14th hospital day the dosage of both mycotics was reduced to one drop each 30 minutes during the day and every three hours throughout the night. The eye, which had exhibited slight improvement on the 9th hospital day, showed definite improvement on the 15th day. The ulcer was smaller, and the hypopyon had begun to clear and was gone in another 24 hours. On the 18th hospital day, the patient had regained much of his sight and oral nystatin was discontinued. On the 21st hospital day, the patient was discharged to home with instructions to continue the nystatin and amphotericin B instillations every hour. The patient has

Fig. 1.—Corneal ulcer before treatment.

Fig. 2.—Eye after treatment with nystatin and amphotericin B locally.



been seen as a follow-up from the hospital at weekly intervals or so by one of us (G. C.), and it was found that the cornea has healed entirely. There is no stain left, and the eye is completely without any signs of reaction (Fig. 2). The pupil is mobile, and there is a dense leukoma covering the central portion of the cornea and extending down into the stroma approximately halfway through the thickness of the cornea. The vision is 20/200 with best possible correction.

Microbiological Studies

Bacteriological studies of a corneal swab taken before the advent of therapy yielded only Bacillus subtilis and Staphylococcus albus (nonvirulent), both of them very sensitive to several antibacterial agents including chloramphenicol.

Specimens for mycological study were taken by curettage and swab of the ulcer on Sept. 8. Potassium hydroxide preparations of the scrapings examined the same day showed numerous hyaline, oval, truncate, single-celled fungus spores, many of them resembling nonbudding yeast cells, and collections of mold hyphae (Fig. 3). Some of the spores were attached terminally to clusters of hyphal stalks, resembling coremia. Gram's and Wright's strains of

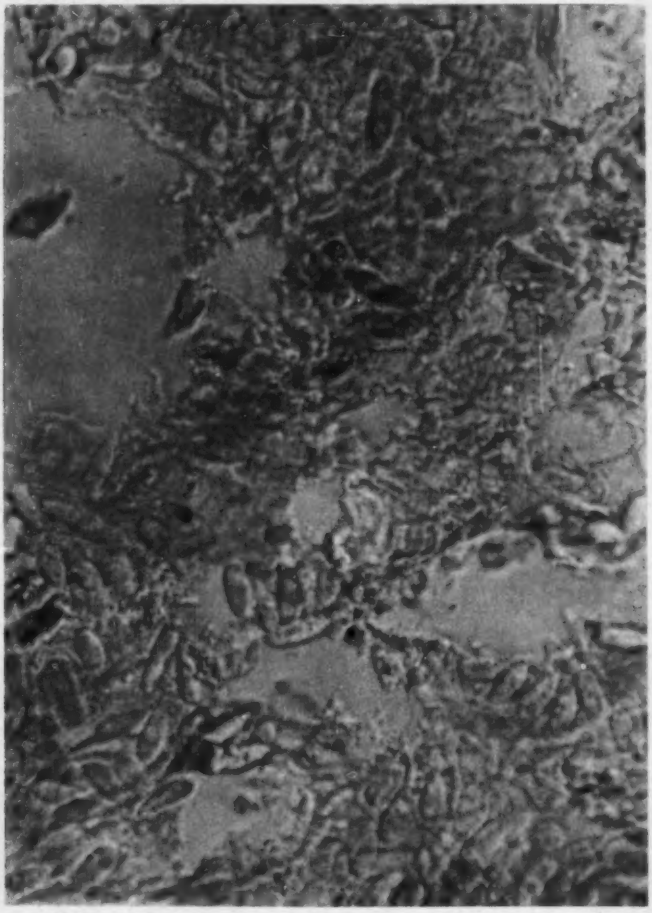


Fig. 3. — Masses of Allescheria boydii conidia in potassium hydroxide preparation of scrapings from corneal ulcer; reduced about 13% from mag. × 550.

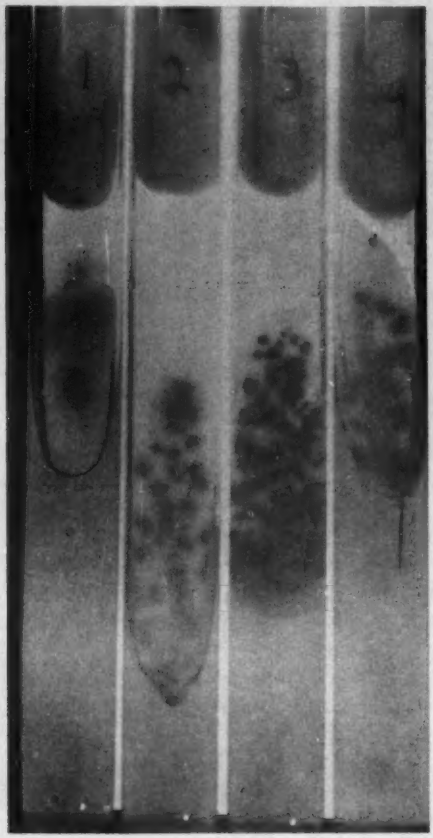


Fig. 4.—Primary cultures taken from the ulcer, showing numerous colonies of A. boydii after three days.

smears prepared from the swabs exhibited Gram-positive hyphal fragments, some branched, and large, Gram-positive, yeast-like, nonbudding cells. One slant of Sabouraud dextrose agar containing penicillin and streptomycin was inoculated with a portion of the scrapings, and three were inoculated directly with the swabs, all of them being incubated at 25 C.

After two days' incubation the Sabouraud slant inoculated with scrapings showed a single grayish-white, cottony mold colony, 4 mm. in diameter, with olivaceous reverse, suggestive of M. apiospermum. The following day the remaining three slants contained numerous tiny, dark-centered, white to grayish mold colonies (Fig. 4). Lactophenol cotton blue mounts of all four slants showed innumerable conidia typical of M. apiospermum (Fig. 5). Nystatin sensitivity tests (Mycostatin Sensitivity Disks, Squibb) indicated sensitivity of the organism to this antibiotic. After three weeks of incubation at room temperature the original Sabouraud agar cultures had formed numerous fertile, dark perithecia characteristic of A. boydii, the ascomycetous stage of M. apiospermum (Fig. 6). These structures also appeared in two weeks upon slants of potato dextrose, corn meal, and Czapek's agar inoculated from the original slants. No

Fig. 5. — Hyphae with attached conidia of A. boydii in lactophenol cotton blue mount from culture; reduced about 38% from mag. × 550.

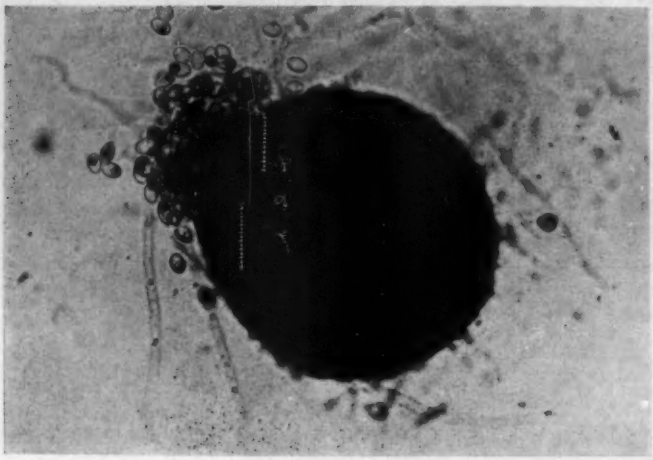


Fig. 6. — Perithecium with ascospores of A. boydii; reduced about 38% from mag. × 550.

coremia have been found after prolonged incubation of all of these cultures.

After institution of antifungal therapy, cultures taken on the third day of treatment with nystatin yielded only two and three mold colonies, respectively, on two Sabouraud slants. Further cultures taken on Sept. 23, one day prior to discharge of the patient from the hospital, yielded no growth.

Comment

Bacteriological studies of material taken from the ulcer before the advent of specific therapy failed to reveal any probable bacterial agent. The evidence of exclusive fungous etiology was reinforced by failure of the lesion to respond to antibacterial therapy, despite the fact that this included chloramphenicol, to which both of the bacterial species cultured proved very sensitive. On the other hand, administration of broad-spectrum antibiotics and steroids may have contributed to the progressive deterioration of the cornea prior to institution of antifungal therapy. Haggerty and Zimmerman [12] recently have emphasized the dangers of applying steroids and antibiotics in local management of acute ocular inflammation, a practice to which they attribute an increasing incidence of fungal diseases of the eye.

Further evidence for a probable primary role of A. boydii in the etiology of corneal ulcer has been adduced by Ley,[13] who found that this organism, as well as C. albicans and A. fumigatus, would cause fungus keratitis when applied together with cortisone to the traumatized cornea of the rabbit. Saprophytic fungi, such as Aspergillus terreus, Cephalosporium, and Geotrichum, produced no lesions under the same conditions. This author also demonstrated the potentiating effects of antibiotics, as well as steroid therapy, in ocular fungus infections and cites many references to the pertinent literature.

Foster et al.[14] achieved favorable results with topical application of amphotericin B in the treatment of experimental ocular fungus infections in rabbits, as well as in one human case. In the present case there was a remarkable response to antifungal antibiotics after more usual therapeutic measures had failed, thus underscoring the necessity for an early and accurate microbiological diagnosis if the eye is to be saved. It is apparent that a search for fungi, including KOH examination and culture, should be instituted early in the management of every case of corneal ulcer, especially in the presence of hypopyon.

Summary

A patient struck in the eye by a fish scale developed corneal ulcer with hypopyon, which was treated with massive doses of broad-spectrum antibacterial drugs to no avail. After the demonstration, by KOH examination, of numerous conidia and hyphae of Allescheria boydii (Monosporium apiospermum) in scrapings from the cornea, instillation of nystatin and amphotericin B resulted in cessation of the infection. Identity of the mold was confirmed by culture.

This is the second known case of corneal ulcer associated with A. boydii and the first in which enucleation of the eye was averted by means of specific antifungal therapy.

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REFERENCES

1. Pautler, E. E.; Roberts, R. W., and Beamer, P. R.: Mycotic Infection of the Eye: Monosporium Apiospermum Associated with Corneal Ulcer, A. M. A. Arch. Ophth. 53:385 (March) 1955.

2. Benham, R. W., and Georg, L. K.: Allescheria Boydii, Causative Agent in a Case of Meningitis, J. Invest. Dermat. 10:99 (March) 1948.

3. Tong, J. L.; Valentine, E. H.; Durrance, J. R.; Wilson, G. M., and Fischer, D. A.: Pulmonary Infection with Allescheria Boydii: Report of a Fatal Case, Am. Rev. Tuberc. 78:604 (Oct.) 1958.

4. Aldridge, J. S., and Kirk, R.: Mycetoma of the Eyelid, Brit. J. Ophth. 24:211 (May) 1940.

5. Ajello, L.: The Isolation of Allescheria Boydii Shear, an Etiologic Agent of Mycetomas, from Soil, Am. J. Trop. Med. 1:227 (March) 1952.

6. Pezenburg, E.: Allescheria Boydii Shear 1921, isoliert aus einer Hautveränderung beim Hund, Mykosen 1:172 (Sept.) 1958.

7. Gordon, M. A.: Nutrition and Sporulation of Allescheria Boydii, J. Bact. 73:199 (Feb.) 1957.

8. Birge, H. L.: Ocular Aspects of Mycotic Infection, A. M. A. Arch. Ophth. 47:354 (March) 1952.

9. Roberts, S. S.: Nystatin in Monilia Keratoconjunctivitis, Am. J. Ophth. 44:108 (July) 1957.

10. Montana, J. A., and Sery, T. W.: Effect of Fungistatic Agents on Corneal Infections with Candida Albicans, A. M. A. Arch. Ophth. 60:1 (July) 1958.

11. Urrets-Zavalia, A., Jr.; Remonda, C., and Ramacciotti, N.: Peculiar Type of Corneal Ulcer Associated with Candida Mycoderma, Am. J. Ophth. 46:170 (Aug.) 1958.

12. Haggerty, T. E., and Zimmerman, L. E.: Mycotic Keratitis, South. M. J. 51:153 (Feb.) 1958.

13. Ley, A. P.: Experimental Fungus Infections of the Cornea, Am. J. Ophth. 42:59 (Oct.) 1956.

14. Foster, J. B. T.; Almeda, E.; Littman, M. L., and Wilson, M. E.: Some Intraocular and Conjunctival Effects of Amphotericin B in Man and in the Rabbit, A. M. A. Arch. Ophth. 60:555 (Oct.) 1958.

Lens Surgery in Marfan's Syndrome

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Marfan's syndrome, arachnodactyly, is a hereditary condition believed to be caused by disease of the connective tissues, mainly a defective production or excess destruction of chondroitin sulfate. The latter is an important ingredient of the ground substance of the connective tissues. All the features characteristic of Marfan's syndrome—kyphoscoliosis, periosteal new bone formation, and dissecting aneurysms of the aorta—have been reproduced in growing rats fed with diets containing 50% sweet-pea pods, a diet which interferes with the effective utilization of chondroitin sulfate. Aneurysmal dilatation of the aortic sinuses are so characteristic of this condition that its presence leads to a presumptive diagnosis of Marfan's syndrome and the search for other stigmata.

Marfan's syndrome is not frequently seen in an average office practice but, when encountered leads to very vexing problems. If dislocated lenses are present, vision is usually very poor and the children are handicapped in their proper development. Not only do they have difficulty in doing their school work, but they also can not see well enough to indulge in normal physical childhood activities. Even when corrected, the very high astigmatic correction usually necessary, is of little help for their visual development. In addition, the shifting lens changes the refraction so that frequent change of glasses may be necessary.

The question of when to operate or whether to operate at all has found divided opinions, preponderately against any form of surgery unless absolutely necessary. Because of this, I believe that my experience in several of these cases is worthy of reporting.

Submitted for publication April 23, 1959.

Read before the Section of Ophthalmology, New York Academy of Medicine, New York, April 20, 1959.

This paper is based on lens surgery in eight eyes of four cases of Marfan's syndrome. Three of the cases were members of one family. These were offspring of two brothers who were typical cases of arachnodactyly with dislocated lenses. According to these two (Case 1 and Case 2), their grandmother wore thick glasses and had poor vision. She had five children, three boys and two girls. Two of the boys wore thick glasses and had poor vision. Nothing else was known about them. The other boy apparently had no ocular difficulties. One of the girls had normal eyes and the other, the mother of Case 1 and Case 2, wore very thick glasses and had poor vision. She bore four children. One son and the only daughter had normal eyes, and so did their children and grandchildren. Of the other two sons, the older, Case 1, had poor vision as a child but was not fitted with glasses until 11 years of age. At 31 years of age, vision in the left eye suddenly became impaired. An iridectomy was done, after which the eye became inflamed and troublesome. Shortly after, that eye had to be operated upon because of glaucoma. According to him that eye had no light perception. At 33 years of age, the lens of the right eye dislocated into the anterior chamber and was successfully removed by the late Dr. Ben Wit Key. Vision in that eye was 20/20 with his aphakic correction. He died of a heart attack about two years ago, aged 54.

The younger brother, Case 2, had very poor vision as a child. When the patient was 16 years of age, the late Dr. Ben Wit Key operated upon the left eye. Examination on Nov. 28, 1943, showed that the

right eye had a cataractous lens which was dislocated upward. The fundus was not visible. Vision was limited to shadows, not correctable. The left eye was aphakic, and the pupil was round and clear. The fundus was normal. Vision with a +14.00 sphere was 20/30. He also died of a heart attack shortly after the older brother, at the age of 45.

The first member of the family treated by me was Case 3, son of Case 2. He was examined on May 16, 1943, at 5 years of age because of vision so poor that he was always tripping over objects. He had a typical Marfan's syndrome with dislocation of both lenses upward and nasally. On May 18, 1943, a discission of the lens was performed in both eyes at the Brooklyn Eye and Ear Hospital. The left lens absorbed poorly, so that discission on that eye was repeated on Aug. 31, 1943. At the present time, his pupils are clear. Vision: Right eye 20/20, with a +12.00 sphere combined with a +2.00 cylinder, axis 75; Left eye 20/20, with a +13.00 sphere combined with a +1.00 cylinder, axis 90. The fundi showed no areas of chorioretinal disease. He is attending college and has had no difficulty keeping up with his studies.

On Feb. 15, 1948, Case 4, the son of Case 1, age 18 months, was brought in for examination. Both irides were tremulous and the lenses dislocated upward and nasally. At 2 years of age, a +11.00 sphere combined with a +2.00 cylinder, axis 180, lens was prescribed for the right eye and a +9.00 sphere combined with a +1.00 cylinder, axis 180, lens for the left. At 5 years of age he had considerable difficulty with his vision, so that the parents were worried about the child injuring himself. On June 15, 1953, a discission on both lenses was done at the Brooklyn Eye and Ear Hospital. Both pupillary areas are clear, and corrected vision is 20/25+ in both eyes. He wears a +11.00 sphere combined with a +1.50 cylinder, axis 90, on the right eye and a +11.00 sphere combined with a +1.00 cylinder, axis 90, on the left eye. The fundi do not show evidence of chorioretinal disease.

The third member of this family, Case 5, daughter of Case 2, was brought to me on Oct. 22, 1945, at 5 months of age. The irides were tremulous and the lenses dislocated upward and nasally. At 3 years of age she was given the following correction: right eye, +4.00 sphere combined with a −9.00 cylinder, axis 180; left eye, +2.00 sphere combined with a −8.00 cylinder, axis 180, for approximately 20/70 vision in both eyes. At 7 years of age, she had 20/30 vision in both eyes with the same correction. She was fairly comfortable and was able to attend school successfully with minor refractive adjustments until the latter part of 1953. At this time, the left lens moved upward slightly so that its lower edge bisected the pupil, giving her double vision. Because of this and also because of the good results obtained in her brother, Case 3, and her cousin, Case 4, the parents wanted surgery. However, I did not feel that there was any urgency and was reluctant to operate. The parents became very insistent, and I decided to present the family and the problem before the New York Society for Clinical Ophthalmology on Feb. 1, 1954.

It was the unanimous opinion of all who expressed their opinions that surgery was absolutely contraindicated because either detachment of the retina, glaucoma, or both would positively follow. In spite of having been informed of the decision, the parents continued to insist on operation. Finally, the mother, who by this time was widowed, practically pleaded for the operation. On June 3, 1957, a discission was done on the left lens and on May 10, 1958, on the right lens, both at the Brooklyn Eye and Ear Hospital. At the present time, her pupils are clear and vision in both eyes with correction is 20/25. She wears on the right eye a +14.00 sphere combined with a +3.00 cylinder, axis 85, and on the left eye, a +14.00 sphere combined with a +2.50 cylinder, axis 75. The fundi show no evidence of chorioretinitis.

The fourth case which I treated, Case 6, a white woman, age 23, was referred on June 20, 1957, because of loss of vision in the left eye. Three weeks before, she felt a pull in the left eye followed by the appearance of a black spot. Subsequently, she lost her vision nasally and, for the past 10 days, completely. She had not had any vision in the right eye as far back as she could remember but had been able to work satisfactorily as a typist.

Examination showed a tall young woman with the typical features of Marfan's syndrome. Vision in the right eye was limited to light perception with good light localization. The iris was tremulous, and the lens was cataractous and dislocated upward. The fundus could not be seen. The left eye had uncertain light perception. The lens was cataractous and displaced upward so that the lower half of the pupil was uncovered. Through this, a large detachment of the upper retina could be made out, but the upper periphery could not be visualized.

On June 24, 1957, a discission of the right lens was done and the left lens removed with a Weber's loop. Only a moderate amount of very fluid vitreous was lost. After an uneventful healing, she was referred to the Retina Clinic at the Massachusetts General Hospital. The report stated that she had fixed retinal folds and several small holes in the extreme upper periphery. Operation was unsuccessful.

In the meantime, the right lens continued to absorb slowly and then stopped. On March 5, 1958, a second discission was performed with excellent results. The fundus which now could easily be seen showed extensive and diffuse chorioretinal degenerative changes. Vision in that eye is 15/400 with a +6.50 sphere combined with a +1.00 cylinder, axis 15. With this, she is able to get around by herself. She is now in a school for the blind, where she was fitted with telescopic lenses which have enabled her to see typewriter print.

Comment

Discission of the lens in the young is a traumatic operation and multiple discissions that much more traumatic. It is well known that after discissions vision and even the eye itself may be lost because of detachment of the retina, glaucoma, and/or iridocyclitis. An important cause for these complications is insufficient opening of the capsule so that not enough cortex is exposed to the dissolving action of the aqueous. This necessitates additional discissions and unnecessary traction on the ciliary processes and ciliary body. This traction may lay the ground work for the complications mentioned above and is even more likely to occur if the lens is partially dislocated, making it a freely movable target and much more difficult to cut.

The technique I have used to avoid much unnecessary movement of the lens and at the same time to do a generous capsulotomy is to spear the lens from one side with a Ziegler Needle and to cut the lens with another needle entered from the other side. In cutting the lens, as much downward movement as possible is avoided to lessen the traction on the zonular fibers and thus indirectly on the ciliary body. The cutting is done toward the needle which is being used as a spear; then the second needle is used as a spear, and the first used to cut with. The lessening of the movement of the lens, in addition to reducing much of the traction on the ciliary body, also avoids much unnecessary stirring up of a vitreous which, in all probability, is already diseased. I believe the technique I have used helps fix the lens and also lessens the movability of the lens, thus enabling one to do a better discission. Only two of the seven eyes in which discission was done had to have the discission repeated and then only once.

I believe that glaucoma and detachments following surgery in these cases is no greater and probably not as great as the same complications occurring in unoperated-on cases. All the statistics reviewed reported a high percentage of serious complications because of glaucoma, retinal detachment, and iridocyclitis in unoperated-on cases. The latest study on a large series

of cases was reported by Watzke. He reported 41 members in four generations of one family; 25 of these had eye complications. He personally examined 11 members, mainly in the fourth generation. Of these, six had vision of 20/70 or less after correction. One eye had to be enucleated because of painful glaucoma due to dislocation of the lens into the vitreous, and one developed a detachment of the retina following intracapsular extraction.

There is no doubt that a freely movable lens must over a period of time cause some reaction. Constant irritation of the anterior face of the vitreous may be the cause for the degeneration of the vitreous and possibly also for the degenerative changes in the choroid and retina. In fact, Watzke mentioned this as a possible cause for the chorioretinal degenerative changes found in many of the adults in his series. In this connection, it is interesting to note that only Case 6, who was a young adult at the time of operation had chorioretinal changes. In the other three cases, who were operated upon at a very young age, the fundi were normal.

Considering all the facets of the problem, I must disagree with those who advocate no surgery as long as these handicapped children are able to get around, which, incidentally, is about all that many of them can do. If we wait until surgery is necessary, it is usually at a much less favorable stage; too often because of serious complications, such as anterior dislocation of the lens, or if cataract develops, an extraction rather than a discission will have to be done. Because the vitreous has degenerated and has become very fluid, extraction is usually doomed to failure, despite the occasional successful case reported.

Bengisio believed that the poor prognosis in lens extraction was due to the mesodermal dysplasia. This dysplasia made extraction more hazardous and was also responsible for the chorioretinal degeneration and spontaneous retinal detachment.

Conclusion

This paper is a plea for early discission in Marfan's syndrome when the dislocated lens is causing visual difficulties. This, more frequently than not, results in better vision and permits a more normal development of the child, mentally, socially, and educationally.

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REFERENCES

1. Ponseti, I. V., and Shepard, R. S.: Lesions of the Skeleton and of Other Mesodermal Tissues in Rats Fed Sweet-Pea (Lathyrus Odoratus) Seeds, J. Bone & Joint Surg. 36-A:1031, 1954.

2. Steinberg, I., and Geller, W.: Aneurysmal Dilatation of the Aortic Sinuses in Arachnodactyly: Diagnosis During Life in 3 Cases, Ann. Int. Med. 43:120, 1955.

3. Steinberg, I.; Mangiardi, J. L., and Noble, W. J.: Aneurysmal Dilatation of the Aortic Sinuses in Marfan's Syndrome, Circulation, 16:368, 1957.

4. Rados, A.: Marfan's Syndrome, Arch. Ophth. 27:477, 1942.

5. Anderson, M., and Pratt-Thomas, H. R.: Marfan's Syndrome, Am. Heart J. 46:911, 1953.

6. Bean, W. B., and Ponseti, I. V.: Dissecting Aneurysm Produced by Diet, Circulation 12:185, 1955.

7. Bengisio, N.: Marfan's Syndrome, Bull. et mem. Soc. franç opht. 70:106, 1957.

8. Watzke, R. C.: Marfan's Syndrome: A Report of Its Inheritance in 4 Generations, A. M. A. Arch. Ophth. 6:492, 1958.

Pupillary Escape in Disease of the Retina or Optic Nerve

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Duke-Elder,[1] in discussing the clinical picture of optic neuritis, mentions "a peculiar pupillary reaction common to all forms of conduction interference, wherein, although both the direct and consensual reactions are present the contraction is not maintained under bright illumination so that the pupil slowly dilates again while the light is still kept upon the eye." This seemingly paradoxical light reaction of the pupil was observed in retrobulbar neuritis by Marcus Gunn (1904), who attributed it to the consensual reaction of the pupil to darkness. In this paper is presented a simple and sensitive method for demonstrating the Marcus Gunn sign and, also, a hypothesis to show that there is nothing peculiar or paradoxical about this pupillary reaction, which should be expected whenever the light sense is reduced by disease of the retina or optic nerve.

Submitted for publication April 18, 1959.

Supported by a research grant from the Kaiser Foundation Hospitals.

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Hypothesis

Assume that the pupillomotor impulses produced by visible light (and hence the stimuli to the pupilloconstrictor center *) are proportional to the visual stimuli and are conveyed by the same visual fibers to the posterior one-third of the optic tracts; then by collaterals to the p. c. c., where the pupillomotor impulses from both retinas are summated. Postulate the existence in the pretectal area of the midbrain of a functionally single p. c. c. from which an equal and simultaneous innervation goes to each

* Pupilloconstrictor center will be abbreviated p. c. c. henceforth.

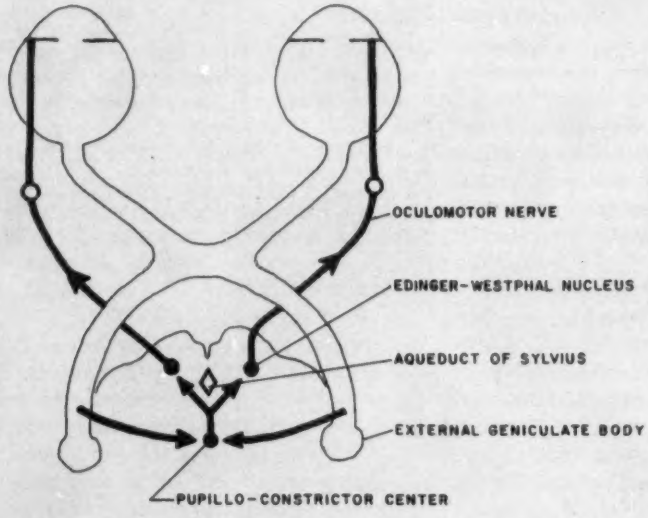

Fig. 1. — The summation of afferent pupillomotor impulses from both optic tracts in a single pupilloconstrictor center (p. c. c.) which then sends the same efferent innervation to each sphincter pupillae muscle simultaneously.

Edinger-Westphal nucleus, thence to each sphincter pupillae muscle via the oculomotor nerves (Fig. 1). Other things being equal (i. e., disregarding the effects of emotion, fatigue, and stimuli from other parts of the central nervous system upon the p. c. c.), the stimulus sent out by the p. c. c. to each sphincter pupillae muscle should be a log function of the intensity of illumination. If visual sensation is decreased by disease of the retina or optic nerve there should be a proportionate decrease in stimuli sent out by the p. c. c.

This hypothesis is based on the following information and thinking:

1. Anatomically, there are two sets of pretectal nuclei, one on each side of the midline. Each is believed to act as a p. c. c., and each is connected to both Edinger-Westphal nuclei. The concept of a functionally single center which sends an equal and simultaneous stimulus to the sphincter muscle of both pupils is borrowed from Hering's law pertaining to the extraocular muscles. It serves to explain one of the most constant phenomena in nature—the fact that persons without intraocular disease or involvement of the autonomic pupil pathways have equal pupils. It is also the simplest explanation of the equal and superimposable curves for the direct and consensual light reaction of the pupils obtained by Otto Lowenstein in his brilliant researches in pupillography.

2. Parsons (1924) suggested[2] that the tonus of the sphincter muscle is the direct result of afferent impulses through the visual paths.

3. According to Thompson (1947),[3] binocular summation of afferent pupillomotor impulses probably occurs at the synapses within either the pretectal or oculomotor nucleus.

4. Reeves (1917) has demonstrated[4] that pupil size is a log function of the intensity of illumination.

5. According to Adler (1953),[5] there can be little question that the rods and cones are the receptors for both the visual and pupillomotor effects of light. He mentions the belief of Hess and of Magitot that the same optic nerve fiber conveys both the visual and the afferent pupillomotor impulses and shows that this phenomenon does not necessarily contravene Müller's law of the specific irritability of a sensory nerve.

Corollaries of this hypothesis are as follows:

1. Light striking the eyes from the side should not give unequal pupils, i. e., no matter what difference exists between the amounts of illumination reaching the two eyes, the pupils should remain of the same size. This was found to be so in human beings by Jones (1949),[6] working in Lowenstein's laboratory. In this case, although the p. c. c. receives an unequal stimulus from the two eyes, summation occurs and the pupils remain equal because the p. c. c. sends out an equal innervation to the two oculomotor nerves.

2. Lesions of the retina or optic nerve should not give unequal pupils. This was found to be so by Lowenstein (1953) in cats[7] and later (1954) in monkeys and man.[8] Here the eye with retinal or optic nerve disease sends a smaller stimulus to the p. c. c. than does the normal eye. Yet there is no anisocoria because after fusion and summation the p. c. c. sends a smaller but equal stimulus to each sphincter pupillae muscle via the oculomotor nerves.

3. A lesion of the retina or optic nerve should give pupils larger than normal for that person in diffuse illumination. This was found to be so by Lowenstein[7,8] in animals and in man. Here fewer afferent stimuli are received by the p. c. c., and therefore fewer efferent stimuli are transmitted via the oculomotor nerves. Doggart (1957) has noted[9] that severe bilateral macular disease is typically associated with sluggishly reacting pupils of larger than average diameter. Within the past three years I have observed four children with acute simultaneous bilateral optic neuritis. All had severe amblyopia with pupils that were equal but so widely dilated that in

each case the parents commented on their large size.

No one has emphasized the value of the Marcus Gunn pupillary sign more than Kestenbaum,[10] who has devised a useful modification of the test called the *pseudoanisocoria sign*. In this test each eye is exposed separately to light for a few seconds and the final size of each pupil is measured, the wider one signifying a retrobulbar lesion in that eye. Unfortunately, it is often difficult to measure the size of a black pupil within a dark brown iris except by strong focal light. Pupillary escape can be revealed dynamically in the following manner.

A Swinging Flashlight Test for Pupillary Escape

As in a routine eye examination, the examiner stands beside the patient, who is seated. The lights are dimmed, and the patient fixes his gaze on a spot on the opposite wall near the ceiling to eliminate the effect of accommodation on the pupils. A pocket flashlight with a bright light is passed back and forth from one eye to the other, the examiner noting the movement of the pupil in the eye that is illuminated. Normally there is a slight, sometimes imperceptible contraction of the illuminated pupil as the light strikes it. In an eye harboring disease of the retina or optic nerve, the pupil slowly dilates while the light is still upon it. A striking contrast occurs as the light is swung back to the normal eye, which shows a marked pupillary contraction. Thus, instead of measuring the final size of the pupil, one observes the direction of movement of the illuminated pupil, which becomes larger in the abnormal eye and smaller in the normal eye. Several passes back and forth with the flashlight may be required before the proper speed is found to bring out the dynamic anisocoria.

It will be noted that this swinging flashlight test is but a cover test in reverse, for while one eye is illuminated, the other is in relative darkness. A squint that is not manifest but is made evident only by breaking up fusion in the cover test is called a heterophoria, or latent squint. Similarly, an anisocoria that is not evident or manifest but is brought out only by breaking up the fusion and summation of afferent impulses to the mesencephalic p. c. c. (as in this reverse cover test) may be called a *latent* anisocoria. Thus a latent anisocoria signifies disease of the retina or optic nerve, the afferent path of the light reflex. In the absence of intraocular disease affecting the iris, a manifest or obvious anisocoria signifies involvement of the sympathetic or parasympathetic nerves innervating the iris, the efferent path of the light reflex.

Lowenstein[8] has shown that partial lesions of the retina or optic nerve cause a "low intensity" reaction to light, i. e., an inextensive, relatively slow contraction of the pupil with an increased latency period and short duration. He noted, "In low intensity reactions the pupil often begins to redilate before the stimulus has come to an end." A little reflection will reveal that the low-intensity reaction of Lowenstein is the pupillographic description of the Marcus Gunn sign. Pupillary escape is then explained by the fact that the p. c. c. sends out less stimulus, since it receives less stimulus because of disease of the retina or optic nerve. The energy outgo cannot exceed the energy input. Marcus Gunn, by covering one eye and testing the other with a light, was breaking up the fusion of afferent impulses from both eyes in the p. c. c., thus allowing the retina and optic nerve of each eye to be tested separately for their effect on the pupil.

Since a positive Marcus Gunn sign is most readily discernible when the difference in light sense of the two eyes is great, it might not be elicited if there was bilateral conduction interference unless one optic nerve was much more involved than the other. In a patient with a chiasmal lesion, studied by me, there was severe amblyopia in the left eye with a positive Marcus Gunn sign in that eye. The vision of the right eye was normal with a small superior temporal con-

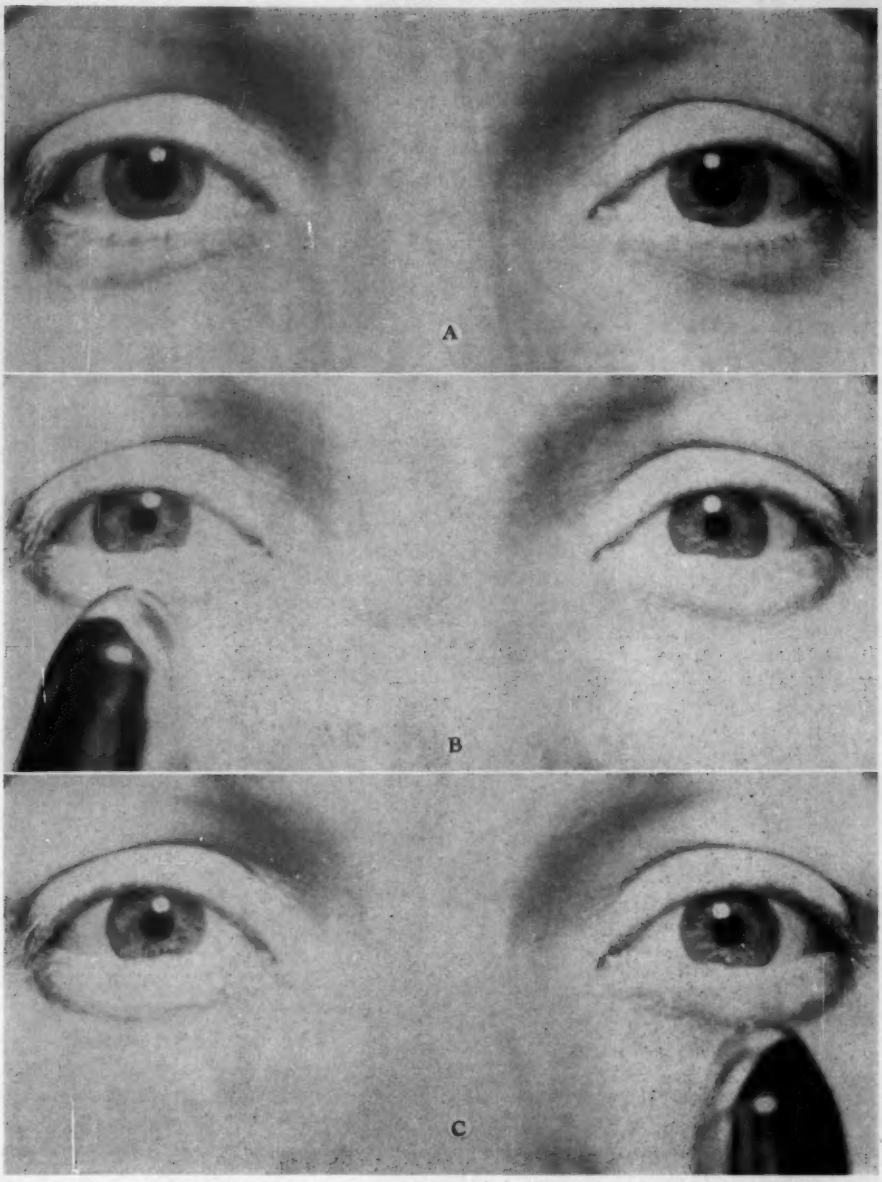

Fig. 2.—Pupillary escape in a patient with multiple sclerosis who had transitory blindness in the left eye two years earlier and now has normal visual acuity and a normal visual field in that eye. *A*, both eyes exposed to weak diffuse illumination; *B*, right eye illuminated by flashlight; *C*, left eye illuminated by flashlight. Note: All photographs were taken with a 35 mm. camera with an electronic flash (1/1000 second). The camera "sees" both eyes simultaneously, revealing that the pupils are always equal. The observer, who watches only the illuminated pupil, sees the pupil in the normal eye in the act of becoming smaller when it is illuminated and the pupil in the abnormal eye in the act of becoming larger when the flashlight is transferred to it—a dynamic anisocoria.

traction of the peripheral field. At operation a chromophobe adenoma of the pituitary gland was found, which completely encircled the left optic nerve and barely touched the undersurface of the right optic nerve. This case confirms the finding of Lowenstein[4] that chiasmal lesions produce bilateral low-intensity reactions to light, but the defect may be more pronounced upon stimulation of one than of the other eye, depending on the site of impairment within the chiasm.

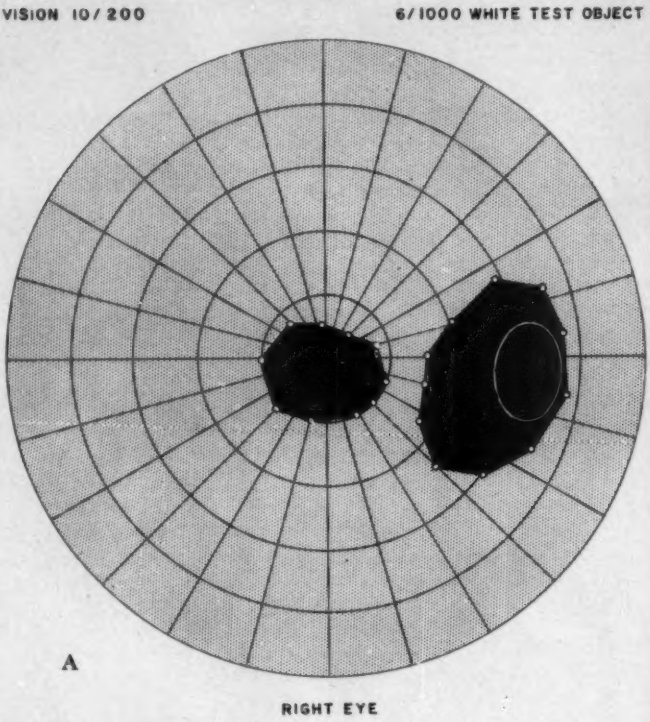

Fig. 3.—Pupillary escape in a patient with multiple sclerosis who had acute retrobulbar neuritis in the right eye five years previously and now has optic atrophy in that eye. *A*, central field showing an enlarged blind spot and an absolute central scotoma surrounded by a large relative scotoma occupying remainder of field, right eye; *B*, both eyes exposed to weak diffuse illumination; *C*, left eye illuminated by flashlight; *D*, right eye illuminated by flashlight.

There are so many ocular abnormalities associated with impaired light sense that the swinging flashlight test has wide application, especially in screening patients with unilateral amblyopia or visual field defect. A positive response is found in the following diseases: (1) optic neuritis, intraocular or retrobulbar; (2) retinal detachment; (3) optic atrophy; (4) direct pressure on the intraorbital or intracranial part of the optic nerve due to a mass lesion; (5) occlusion of the central retinal artery or vein or their branches; (6) other widespread organic disease of the retina. In all these conditions the more extensive the lesion, the greater the impairment of light sense and the more striking the Marcus Gunn sign becomes in an apparently quantitative manner. A negative response is obtained in amblyopia ex anopsia, cataracts, and papilledema due to increased intracranial pressure—a fact which serves to differentiate papilledema of this source from optic neuritis. The response is also negative in mild, short-lived cases of central serous retinopathy which show only metamorphopsia, but a positive response may frequently be elicited in the more severe chronic cases with a relative central scotoma. Glaucoma is associated with a reduced light sense, but the mydriasis due to the increased intra-

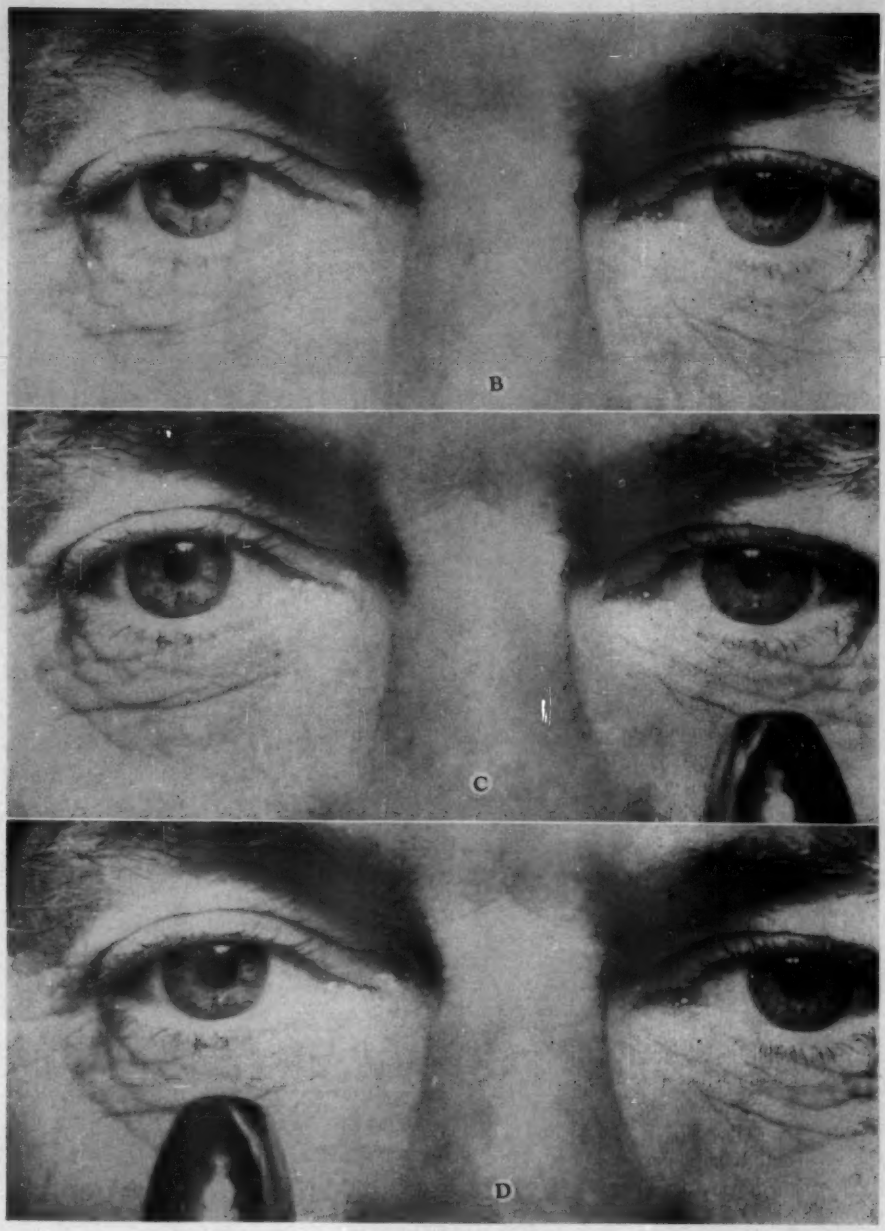

Fig. 3.—(*Continued.*)

ocular tension interferes with the demonstration of pupillary escape.

The usefulness of the swinging flashlight test is illustrated by the following cases.

CASE 1.—A 28-year-old housewife noted blurred vision in both eyes, preceded by "gorgeous colors." By next morning vision in the right eye was normal and in the left eye was reduced to light perception. The fundi were normal and the pupils were equal, but the left scarcely reacted to direct illumination. In 10 days vision improved to 1/200 with a large centrocecal scotoma and a positive Marcus Gunn sign. Two months later the visual acuity and visual fields in this eye were normal. A defect in color perception determined by the Ishihara color charts disappeared six months later. Neurologic examination revealed a positive right Hoffman sign and absent abdominal reflexes. There was a history of numbness of the right half of the body for six weeks, seven years earlier, followed three years later by numbness of the left side of the body lasting three weeks. A diagnosis of acute retrobulbar neuritis secondary to multiple sclerosis was made.

Ophthalmologic examination two years after the episode of blindness revealed a normal left eye except for slight temporal pallor of the disc. The swinging flashlight test, however, showed marked pupillary escape (Fig. 2). The case confirms the observation of Lowenstein [11] that low-intensity reactions are sometimes found after an episode of retrobulbar neuritis even though the visual fields have become normal, thus serving as an objective sign of multiple sclerosis when transitory blindness in the patient's history points to this possibility.

CASE 2.—A 43-year-old schoolteacher with a history of rheumatic mitral valvu-

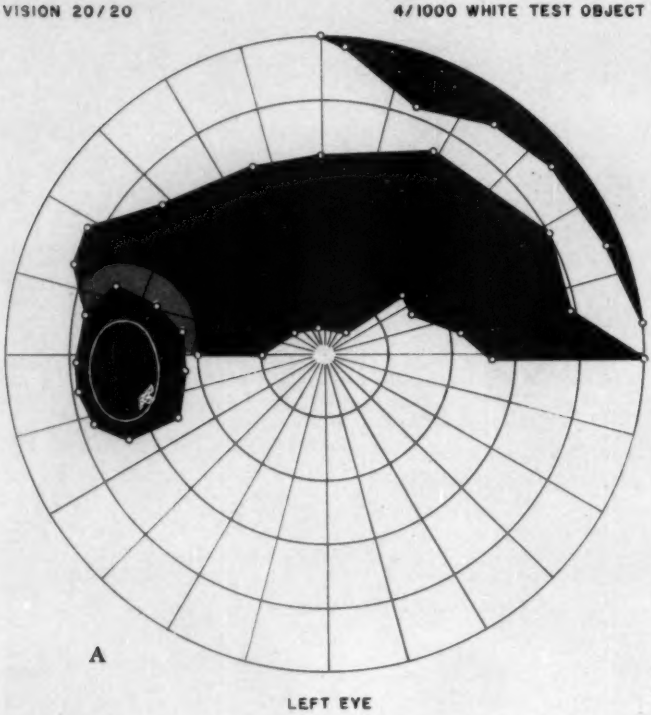

Fig. 4. — Pupillary escape in partial optic atrophy secondary to occlusion of the inferior temporal artery of the left eye four years earlier. *A*, central field showing a superior Bjerrum scotoma with a bridge of relative scotoma between the blind spot and the remainder of the absolute scotoma, left eye; *B*, both eyes exposed to diffuse illumination; *C*, right eye illuminated; *D*, left eye illuminated.

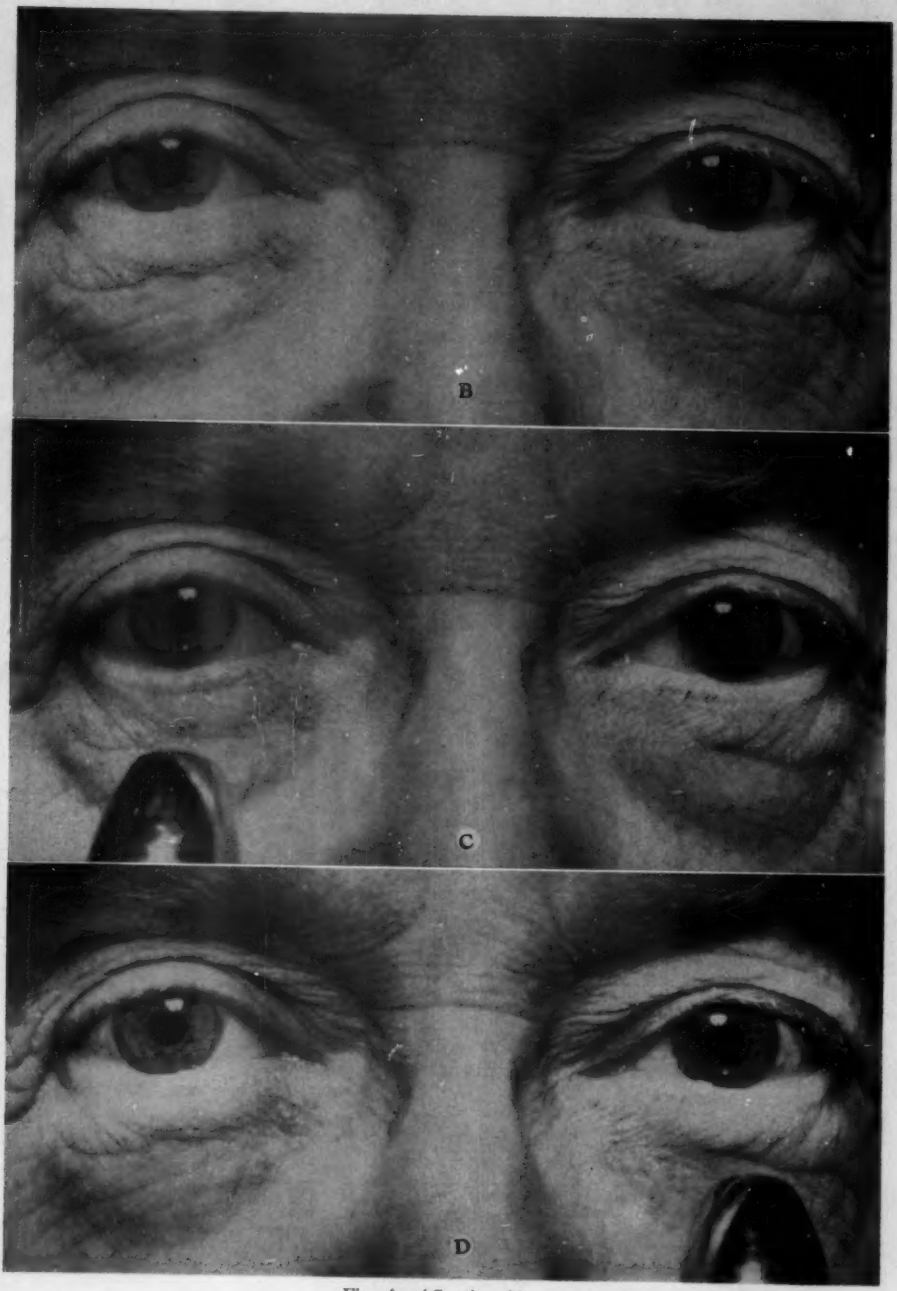

Fig. 4.—(*Continued.*)

litis noted a "blind spot" in the vision of his right eye. The fundi were normal, but there was a central scotoma in the right eye; vision was reduced to 20/200, and the Marcus Gunn sign was positive. Four months previously he had noted numbness of both legs lasting five weeks. Neurologic examination revealed absent right abdominal reflexes, a hyperactive right knee jerk, and a bilateral Babinski sign. The spinal fluid protein was 55 mg. per 100 ml. Two months later, definite temporal pallor of the right disc appeared and both abdominal reflexes were absent. A diagnosis of multiple sclerosis was made. Five years later the vision in the right eye was 17/200 (excentric) with a completely pale optic disc. Central fields revealed an enlarged blind spot and an absolute central scotoma of 4 degrees surrounded by a large relative scotoma involving the remainder of the central field. Pupillary escape was easily shown by the swinging flashlight test (Fig. 3).

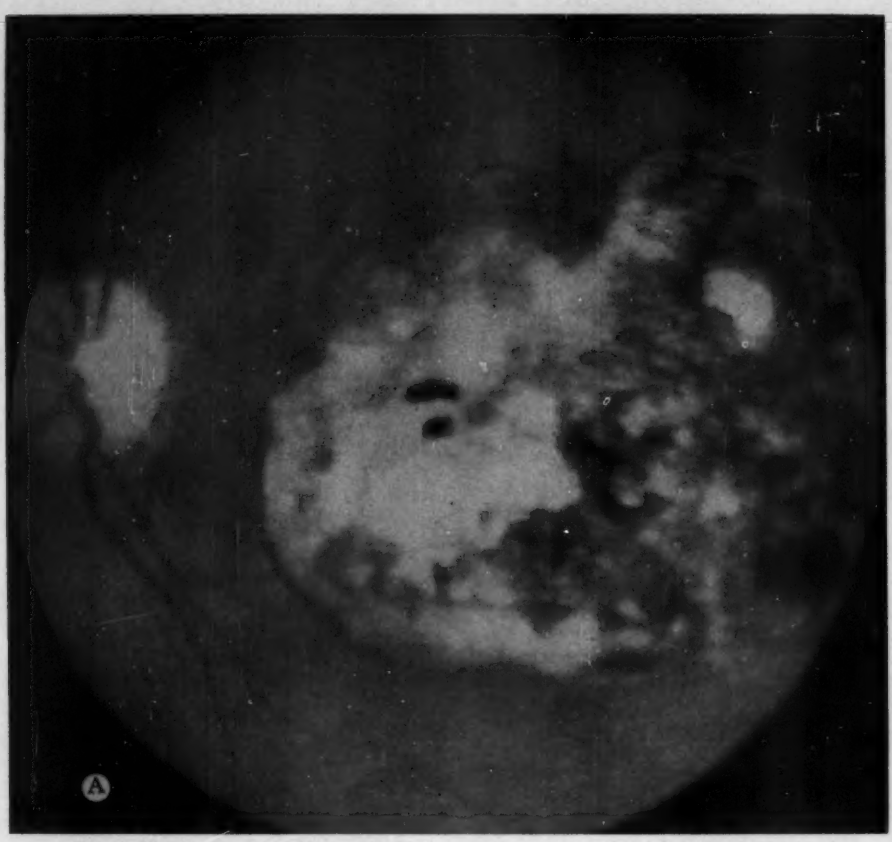

Fig. 5.—Pupillary escape due to left central chorioretinitis. *A*, retinal photograph showing large area of old healed central chorioretinitis, left eye; *B*, both eyes illuminated; *C*, right eye illuminated; *D*, left eye illuminated.

CASE 3.—A schoolteacher, previously healthy, age 62, noted the sudden onset of loss of the upper field of vision in her left eye. When seen 21 hours later, the retina showed the typical picture of acute occlusion of the inferior temporal artery. Most

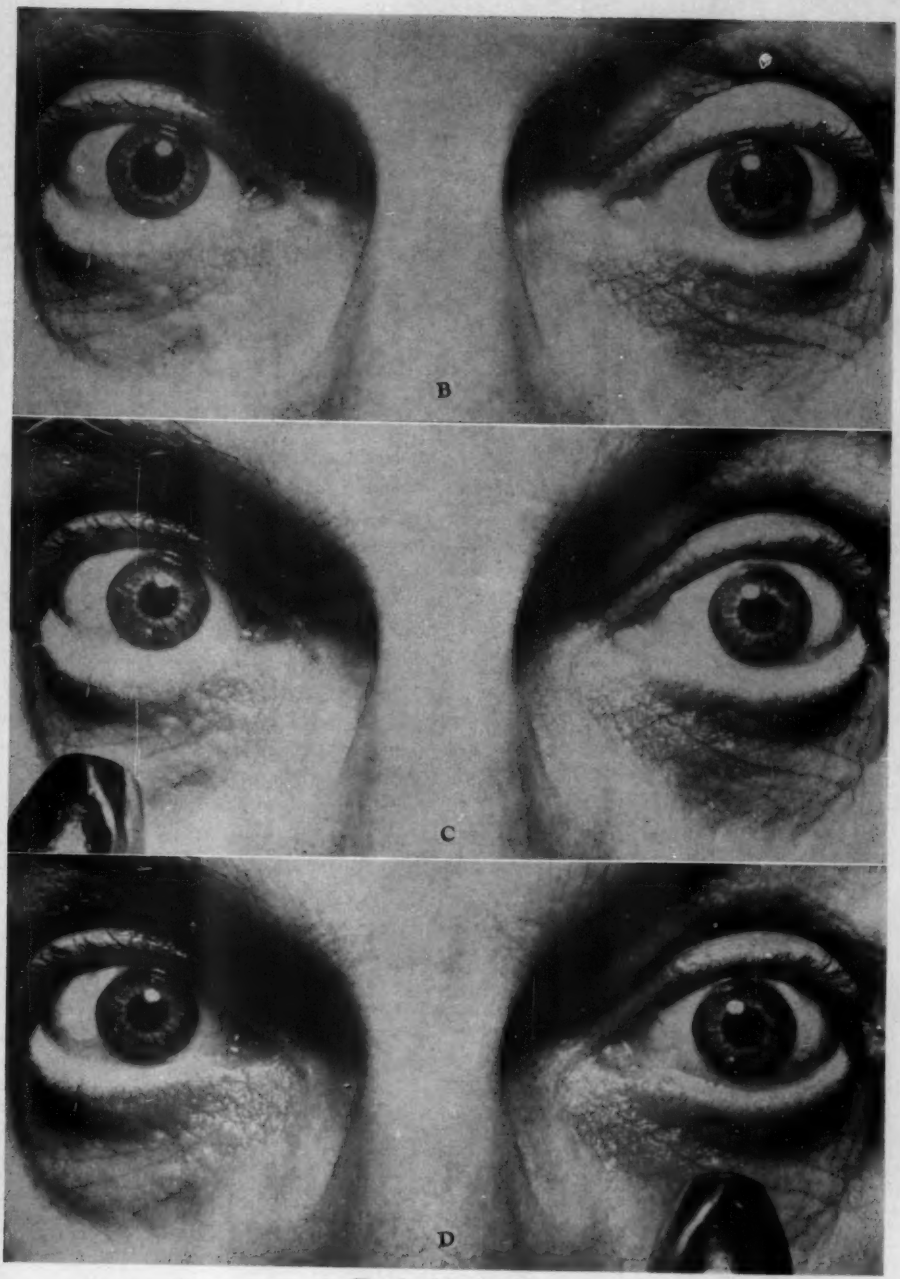

Fig. 5.—(*Continued.*)

of the inferior temporal quadrant of the retina was involved in milky white edema. There was a white plaque on the inferior temporal artery near the disc, and much spasm was present in the artery. The right eye showed retinal arteriosclerosis. Four years later the peripheral field of the left eye showed only a slight contraction in the superior nasal quadrant; the central field showed a superior Bjerrum scotoma. There were localized narrowings in the inferior temporal retinal artery, which had a white sheath near the disc. A positive Marcus Gunn sign was readily obtained with the swinging flashlight test (Fig. 4).

CASE 4.—A 57-year-old restaurant manager stated that he had lost the central vision in his left eye when he contracted smallpox at the age of 17. Examination revealed a large area of old healed central chorioretinitis in the left eye (vision 20/200, excentric). Latent anisocoria was demonstrated easily by the reverse cover test with the flashlight (Fig. 5).

Summary and Conclusions

A hypothesis of pupillary action is presented, based on analogy with extraocular muscle action and depending on equal and simultaneous innervation to the sphincter pupillae muscles from a functionally single center for pupil constriction. Other things being equal, the afferent pupillomotor impulses to this center are proportional to the visual sensations elaborated in the retinas and are summated in the pupilloconstrictor center, to which they are conveyed by collaterals from the optic tracts. Any disease of the retina or optic nerve which decreases the light sense correspondingly decreases the afferent impulses to the p. c. c., resulting in the same decreased innervation to each sphincter pupillae muscle.

Corollaries of this postulate are (1) unequal illumination of the eyes does not cause anisocoria and (2) a lesion of the retina or optic nerve is associated with equal but larger pupils—facts proved by Lowenstein and his co-workers.

The term *latent anisocoria* (analogous to latent squint) is proposed to describe the pupil phenomenon in disease of the retina or optic nerve, for the pupils are equal, but an abnormality is revealed when fusion is broken up by the cover test. Thus, the Marcus Gunn sign represents a latent anisocoria due to impaired light sense, the p. c. c. sending out less stimulus because it receives less stimulus. In the language of pupillography, an eye showing pupillary escape would show the low-intensity reaction of Lowenstein.

The Marcus Gunn test can be made very sensitive, and pupillary escape may be elicited in a dynamic manner by the use of a swinging flashlight test. With this technique, which is a cover test in reverse, pupillary escape may be demonstrated in optic neuritis, retinal detachment, optic atrophy, direct pressure on the optic nerve, and vascular occlusive and other extensive organic disease of the retina.

Photographs are shown to illustrate the value of this objective test in detecting unilateral impairment of light sense in two retinal and two optic nerve lesions.

280 MacArthur Blvd., W.

REFERENCES

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 3, St. Louis, The C. V. Mosby Company, 1945, p. 2975.

2. Parsons, J. H.: Discussion on the Physiology and Pathology of the Pupil Reactions, Tr. Ophth. Soc. U. Kingdom 44:1-11, 1924.

3. Thompson, L. C.: Binocular Summation Within the Nervous Pathways of the Pupillary Light Reflex, J. Physiol. 106:59-65, 1947.

4. Reeves, P.: Rate of Pupillary Dilatation and Contraction, Psychol. Rev. 25:330-340, 1917.

5. Adler, F. H.: Physiology of the Eye, Ed. 2, St. Louis, The C. V. Mosby Company, 1953, p. 160.

6. Jones, I. S.: Anisocoria: Attempted Induction by Unilateral Illumination, Arch. Ophth. 42:249-253, 1949.

7. Lowenstein, O.; Murphy, S. B., and Lowenfeld, I. E.: Functional Evaluation of the Pupillary Light Reflex Pathways: Experimental Pupillographic Studies in Cats, A. M. A. Arch. Ophth. 49:656-670, 1953.

8. Lowenstein, O.: Clinical Pupillary Symptoms in Lesions of the Optic Nerve, Optic Chiasm, and Optic Tract, A. M. A. Arch. Ophth. 52:385-403, 1954.

9. Doggart, J. H.: Classification and Investigation of Macular Lesions in Everyday Practice, Lancet 1:201-204, 1957.

10. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1946, p. 290.

11. Lowenstein, O., and Lowenfeld, I. E.: Electronic Pupillography, A. M. A. Arch. Ophth. 59: 352-363, 1958.

The Antibacterial Property of Vitreous

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Shafer[1] first reported that if human vitreous is infected with organisms and stored at 4 C it tends to become sterile. We[2] confirmed this observation with use of several pathogenic organisms. Shafer[3,4] then showed that there was a diffusible antibacterial substance in human vitreous which will produce a zone of inhibited growth around pools of vitreous on blood agar plates growing Staphylococcus pyogenes var. aureus, Koch-Weeks bacillus, Proteus vulgaris, and Pseudomonas aeruginosa. This communication confirms Shafer's findings and shows that the diffusible substance could be lyzozyme, since it appears to be active against Micrococcus lysodeikticus.

Experiment

Nutrient agar culture plates were prepared. Ditches were cut out and filled with equal parts of pooled human vitreous and double-strength agar. Thin layers of melted single-strength agar were floated across the top of the ditch plate. Streak cultures of the following organisms were made across the ditch in the following order from above down: M. lysodeikticus, S. pyogenes var. aureus (Wood 46 strain), Escherichia coli, and Acidobacterium aerogenes. After 24 hours of incubation M. lysodeikticus and S. pyogenes var. aureus showed an inhibition zone in the region of the ditch, whereas both E. coli and A. aerogenes showed a confluent growth across the ditch (Figure).

After four days of incubation the results were unchanged. This experiment was repeated on a number of occasions.

Submitted for publication March 17, 1959.

Departments of Ophthalmology (Dr. Reed) and Bacteriology (Mr. Tushingham), University of Manitoba.

A culture plate showing the inhibition zones. The organisms were plated in the following order from above down: M. lysodeikticus, S. pyogenes var. aureus (Wood 46), E. coli, A. aerogenes.

A second series of experiments were carried out in which the effect of the following six fluids were compared: isotonic saline, human vitreous, cerebrospinal fluid, dog vitreous, human blood serum, and rabbit vitreous. Four plates were prepared in the following manner: 25 ml. of agar were poured into a Petri dish. Six discs 6 mm. in diameter were cut out of the agar. One drop of each of the fluids was placed in each cup. The cup was then filled with agar, and, after it solidified, a thin layer of agar was spread over the whole plate. Each plate was inoculated with one of the above-mentioned organisms. After 24 hours of incubation, zones of inhibition were present around the sites of human vitreous on plates inoculated with M. lysodeikticus and S. pyogenes var. aureus only. The other fluids contained no inhibitory substance, and the human vitreous did not inhibit the Gram-negative organisms.

Summary

Our experiments confirmed previous observations that human vitreous contains a substance which has an inhibitory effect upon the growth of some bacteria. They also suggest that this substance is absent in isotonic saline, cerebrospinal fluid, dog vitreous, rabbit vitreous, and human serum.

The fact that the inhibitory substance in human vitreous inhibits Micrococcus lysodeikticus suggests that it could be lysozyme.

We wish to thank Dr. Peter Warner of the Department of Bacteriology, University of Manitoba, for helpful criticism.

Department of Ophthalmology, Winnipeg Clinic, St. Mary's and Vaughan (1).

REFERENCES

1. Shafer, D. M.: Tr. Am. Acad. Ophth. 61: 194 (March-April) 1957.
2. Reed, H.; Wilt, J. C., and Tushingham, G.: A. M. A. Arch. Ophth. 60:361 (Sept.) 1958.
3. Shafer, D. M., and Bussey, J. L.: A. M. A. Arch. Ophth. 60:255 (Aug.) 1958.
4. Bussey, J. L.; Shafer, D. M., and Hughes, I. A.: A. M. A. Arch. Ophth. 61:233 (Feb.) 1959.

Prevention of Herpes Corneae in Rabbits

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Herpes corneae is a common eye disease, and it is often a disabling one. For years much has been written about the interrelationships of the viruses of herpes simplex, herpes zoster, and varicella. Herpetic lesions of the cornea were always intriguing to me for several reasons: They did not respond well to therapy; they occurred often in children; they were usually unilateral, and after some years they seemed to have lost their original severity. More importantly, only rarely had I ever seen a patient who had had a varicella with severe skin manifestations who thereafter had herpes labialis or herpes corneae or herpes zoster. The thought occurred that perhaps there might be some cross immunization and that infections with varicella virus were protective against herpes infections.

More than 90% of the population over 15 years of age possess neutralizing antibodies to herpes virus. Only a small group of the immunizing attacks are clinically recognizable as stomatitis with systemic symptoms in children or pharyngitis with regional lymphadenopathy and systemic symptoms in adults. Apparently the virus thereafter lies dormant in the various body tissues and may be subsequently aroused, but the mechanism of reactivity is disputed.

In this series of studies over a period of nearly three years no attempt was made to identify different strains of varicella or herpes virus nor to determine the virus concentrations in the various inocula. All viruses were obtained from patients infected with herpes labialis and/or corneae and from those with varicella.

The plan of study was rather simple. The rabbits were divided into three groups, A, B, and C. The first two groups of 10 rabbits each, Groups A and B, were given one attack of herpes corneae (there were no failures in takes); in one month, after only those in Group B had recovered from the herpes corneae attack experimentally induced, they were given an intracutaneous abdominal injection of varicella virus, 0.1 cc. (The right eye was used on all rabbits.)

Another group of rabbits, Group C, with no previously induced corneal herpes infection were also given similar intracutaneous varicella injections of 0.1 cc. aspirated from a varicella vesicle.

Three different types of reactions resulted: Group B-1 or Group C-1: those who developed a localized pustule which varied in size from a small pea to a sloughing necrotic area as large as a silver dollar; Group B-2 or Group C-2: those who developed a meningoencephalitis with or without a localized pustule and died (no recoveries); Group B-3 or Group C-3: those who developed nothing.

One month after the local pustule had healed or no pustule had formed, a herpes corneae inoculation was made again on all remaining rabbits as follows: 10 in Group A; 5 in Group B-1; 6 in Group C-1; 2 in Group B-3; 5 in Group C-3. All rabbits in Group B-1 and Group B-3 were easily infected with one inoculation, but their course was milder than their original one. Several months later second inoculations were successful in three rabbits in Group B-1 and one in Group B-3. In Group C-1 no original inoculations or subsequent ones several months later were successful. In Group C-3 two original inoculations were successful and none subsequently. In Group A, all but one second corneal inoculation were successful originally and six were positive in subsequent inoculations (Table).

Submitted for publication April 14, 1959.

Results of Experiment

Groups	Takes
Group A: 10 rabbits	
Previous herpes + 2d inoc. after 1 mo.	9 (90%) mild
Later herpes inoc.	6 (60%) mild
Group B-1: 5 rabbits	
Previous herpes + varicella pustule + subsequent herpes	5 (100%) mild
Later herpes inoc.	3 (60%) mild
Group B-3: 2 rabbits	
Previous herpes + varicella inoc. but no pustule + subsequent herpes inoc.	2 (100%) mild
Later herpes inoc.	1 (50%) mild
Group C-1: 6 rabbits	
No herpes: varicella pustule + subsequent herpes inoc.	0 (0%)
2d herpes inoc.	0 (0%)
Group C-3: 5 rabbits	
No herpes: varicella inoc. but no pustule + subsequent herpes inoc.	2 (40%)
2d herpes inoc.	0 (0%)

Comment

From the above results certain guiding facts may be deduced. It would seem that intracutaneous abdominal injections of varicella virus in rabbits, resulting in a skin manifestation, protect these rabbits from subsequent attempts to produce experimental herpes corneae, but this protection is poor if no skin manifestation had been produced or if the rabbits had been given a previous experimental herpes corneae. The inference is that only if the varicella infection precedes the herpetic one is good protection against a subsequent herpetic one assured.

No attempts were made to determine if the corneal protection was due to circulating antibodies or not, but this would be an interesting study, since so many feel the corneal resistance to herpes when it exists is due to local corneal factors. This may be true, but these factors may not necessarily be locally induced, since in these studies an intracutaneous lesion distant from the cornea seemed to afford protection in one group and the ease of reinfection was apparent in others. Of course, different strains were probably involved, since so many sources of viruses were used.

After having reviewed this work, Dr. Irving Leopold, in a written communication, states: "If an incipient varicella contact does protect, it might mean that it is doing so either by a generally systemic immunity which could protect the cornea (which seems rather difficult to believe) or by the interference whereby one virus by generalized systemic spread (in this case non-pathogenic) occupies all available sites of the tissues which are thereby 'immune' to attack by another virus." This interference explanation certainly seems plausible and applicable here.

The odd fact that apparent protection was afforded only if the varicella inoculum preceded the herpetic one is interesting. This might help to explain why one occasionally sees a patient with herpes corneae who has had a rather severe cutaneous varicella. Here an early systemic herpetic infection could have preceded the varicella and by occupation of so many cell sites itself has blocked out the interference mechanism of a later varicella infection, with the dormant herpetic virus later reactivated and aroused. Some cells may have a peculiar exclusiveness about harboring some related viruses or their products, yielding to squatters' right; first come, first allowed. Unfortunately some viruses are not so appreciative of the cell hospitality as others and later rebel against their hosts, while others remain forever thankful and peaceful and even protective.

In the past, animal transference of varicella (and zoster) virus has been said to be impossible. It was certainly easy in these studies, but no case of generalized rabbit varicella did occur. And no attempt was made to recover, to identify, and to transfer the virus from one rabbit to another. I was unable to secure cultures of varicella virus, but if in the future this virus can be cultivated artificially, inoculation of some such, either the pure varicella type or a mutant type, to small children to give a localized pustule to protect not only against subsequent varicella infections but herpetic ones too certainly appears as a possibility. Of course, there are bacteriological and immunological problems to be

solved and some medicolegal aspects to be worked out, but these should not be insurmountable, since systemic manifestations with varicella are uncommon in young children.

This study is far from conclusive, but it is hoped that it will stimulate others with more elaborate laboratory facilities to pursue it further.

No bibliography has been appended, for anyone interested can readily approach any number of bibliography services and uncover enough to read for a few months. In the February, 1959, issue of the A. M. A. ARCHIVES OF OPHTHALMOLOGY (61:308) is a review on Cornea and Sclera by Leonard Christensen, who lists some interesting bibliography on pp. 326-327, nos. 24-45.

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Mutations of the Retinal Pigment Cells in a Case of Pseudoglioma

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Introduction

Among the most striking cells in diseases of the retina, especially where pseudogliomata are concerned, are the fatty granular cells, generally believed to be fat phagocytes. Coats (1908) believed they were degenerate leukocytes; Leber (1915) said they were derived from the pigment epithelium; Marshall and Michaelson (1933) believed them to be reticuloendothelial cells, and there have been other less likely suggestions. Each point of view has had its supporters.

Despite the fact that pseudogliomata are fairly commonplace in India, there emerges from the case to be reported here several interesting features, although that dealing with the retinal pigment epithelium seems the most important; the present study supports Leber's view as to the origin of the fatty granular cells.

Clinical Description

A boy aged 12 attended with grossly defective vision in both eyes. This history dated back for a year only. The onset had been abrupt. Fundus examination revealed an extensive retinal detachment involving all quadrants in the right eye. The vitreous was conical, a yellowish mass appearing to have pushed the retina forward. There were many small hemorrhages, some ringed with pigment, and several glistening crystalline spots. The picture in the left eye was identical, except that the upper nasal quadrant of the retina was not detached.

Slit-lamp examination revealed no sign of anterior uveal inflammation; there were no tumor deposits on the iris, nor was there a flocculent hypopyon. Tension was not raised, standing at 20 mm. Hg. On transillumination, we decided there was no shadow. The family history was not suggestive, and systemic and laboratory examinations (skiagrams, serological tests, etc.) uncovered nothing. It was concluded that the diagnosis lay between that of a neuroepiblastic tumor and a postinflammatory detachment such as one might get with one of the lesions classified under the head of Coats' disease.

Biopsy by the Posterior Route

It is notable in the literature that in the majority of cases of Coats' disease examined microscopically the eye was excised because the surgeon could not take the risk that he was not dealing with a glioma. In eyes so hopelessly blind as the right one in this case, the loss does not matter of course, except esthetically; nevertheless, to subject a patient to such mutilation unnecessarily, especially where both eyes are involved, is unfortunate, to say the least of it. As a result we tried to assess the value of carrying out a biopsy by the posterior route in the hope that it might furnish information of a reliable kind. A simple diathermy operation was carried out on the right eye, as for a detachment, during which a sample of the subretinal fluid was collected and a biopsy taken through all three coats with a trephine. The fluid was found to be serofibrinous, and the biopsy revealed the presence of fatty granular cells and (as far as it went) the absence of tumor cells. In short, here was

Submitted for publication April 24, 1959.

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added evidence supporting the diagnosis that we were dealing with a pseudoglioma. The eye was then excised to confirm this view in the hope that, if correct, such biopsies might in future help us to make a diagnosis without resource to enucleation. We believe the diathermic nature of the technique would make the risk of local extension of a tumor (if tumor it be) negligible.

Microscopic Appearance of the Whole Eye

The biopsy report confirmed that we were not dealing with a glioma. However, it must be admitted that we could not state categorically that we were dealing with a Coats' disease, although the appearance was highly suggestive. The subretinal exudate, ghost cells, gliosis of the retina with, in places, cystic degeneration, the many retinal hemorrhages, and so on, all supported this view. On the other hand, it was impossible to rule out a pseudoglioma resulting from an inflammatory uveitis, or a toxoplasmosis—not long established as a clinical entity in India by means of the Toxoplasma dye tests—or even a nematode endophthalmitis, especially as there were several eosinophil leukocytes present in the subretinal fluid. Despite these possibilities, however, we believe we are right in categorizing this as a manifestation of Coats' disease. Pathologically, such cases appear to fall into two categories: those where the choroid is normal, where the pigment epithelium is normal, where retinal hemorrhages play a minor role, and where there are many ghost cells, and others where roughly the opposite is the case. The common factor to all is the presence of a subretinal exudate (that is, between the two layers of the primary optic cup), so that it is right for the term "exudative" to appear whether we believe the lesion to be a retinitis, as Coats believed, or a choroiditis. Wolff (1951) was the first to suggest that the original lesion was a choroiditis. In our case there were many chronic inflammatory cells present here and there in the choroid, and a narrow pedicle passed from the choroid into the vitreous through the retina in the manner suggested by Wolff. Along this pedicle migrating pigment and fibrous tissue (additional to glial tissue) could be seen. We had, then, the classical appearance of a Coats' disease, as described by Coats, with, as an addition, an abnormal choroid, as described by Wolff.

Mutations of the Retinal Pigment Epithelium

At the start of this report we said that the most striking cells in diseases of the retina were the fatty granular cells, called "ghost" cells by Coats, and by Marshall and Michaelson "bladder" cells. In the present case this was equally true. Every cell in the retinal pigment epithelium was clumped. This, of course, is the earliest reaction of the pigment cells of the retina to any adverse circumstance and is not specific in itself. However, there were other more advanced changes. At intervals along the epithelium there appeared localized proliferations of the pigment cells closely resembling colloid bodies or drusen; indeed, broadly speaking, they must be categorized as that. They did not resemble the colloid bodies usually described, which are hyaline depositions on the cuticular layer of the membrane of Bruch, nor were they the laminated type of drusen described as being found in association with long-standing detachments; the duration of this case (one year) in that context is not long enough for that anyway. However, these localized aggregations of pigment could be classified under the third type of colloid body described, namely, where lipoidal degeneration of the retinal pigment epithelium has occurred. In that sense these structures were colloid bodies, for the core was never laminated or hyalinized, always revealing the presence of partly depigmented and fat-swollen pigment cells (Fig. 1). Whether we categorize these structures as colloid bodies or not is, in fact, beside the point. The important matter is that it was only at

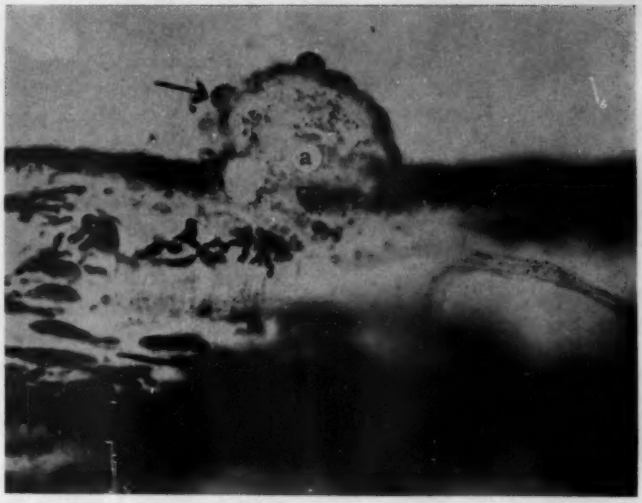

Fig. 1.—Lipoidal degeneration of the retinal pigment cells in localized areas of the retina was a feature. The core of such colloid-like bodies always revealed partly depigmented and fat-swollen pigment cells (*a*). Also shown are retinal pigment cells breaking away into subretinal space (arrow). Hematoxylin and eosin; reduced about 25% from mag. × 200.

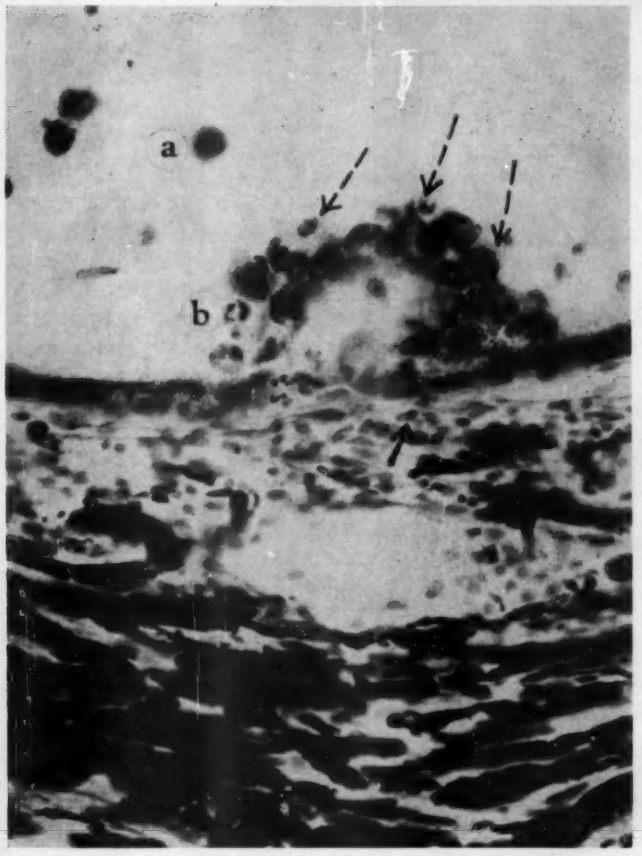

Fig. 2.—Infiltration of the choroid with chronic inflammatory cells (arrow) at the site of the retinal pigment epithelial mutations was the rule. Free clump cell (*a*); retinal pigment cell which has lost a lot of pigment (*b*); also shown are clumped retinal pigment cells breaking away from "colloid body" into subretinal fluid (broken arrow). Hematoxylin and eosin; × 200.

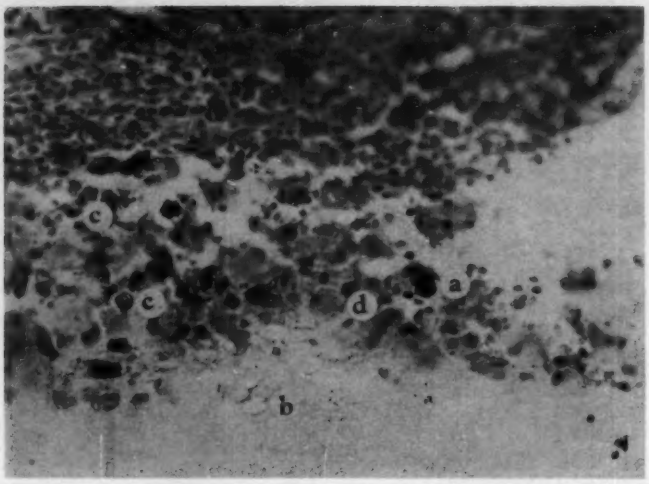

Fig. 3.—Lying free in the subretinal fluid, the different mutations between the clumped pigment cell (*a*) and the bladder cell (*b*) can be seen. Transitory forms (*c*); typical free fat phagocyte with few pigment granules left and swollen with fat droplets (*d*). Hematoxylin and eosin; reduced about 25% from mag. × 180.

these sites that the transient forms between the pigmented clump cell and the rounded depigmented fatty granular cell were found; moreover, inflammation of the choroid occurred predominantly immediately in the vicinity of such lesions (Fig. 2). The different mutations between the fixed pigment cell and the ghost or bladder cell, as might be expected, could also be found in cells lying in the subretinal fluid (Fig. 3). Some workers believe that these same bladder cells can even become multinucleated giant cells, but we could not be sure of that. The many giant-cell forms present (Fig. 4) might have been a reaction to the small extravasations of blood which lay plentifully in the gliosed retina. On the other hand, such was the ease with which the retinal pigment epithelial cell altered its character to that of a free round fat phagocyte with a well-marked nucleus lying in a pigment-free cytoplasm that the further change required to convert it into a giant cell would not be remarkable. It seems that either the cell dies, whereafter the nucleus is extruded and a bladder cell formed, or it might enter an even more

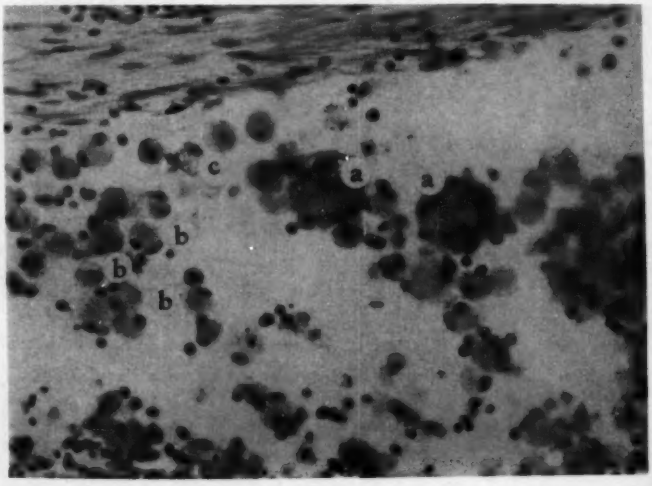

Fig. 4. — Whether or not the many giant-cell forms present (*a*) were further conversions from the typical free fat phagocytes (*b*) derived from the retinal pigment epithelium could not be ascertained. Degenerate fat phagocyte with extruded nucleus (*c*). Hematoxylin and eosin; reduced about 25% from mag. × 200.

active phase of life as a giant cell, but this last is conjecture.

The behavior of the pigment epithelium in retinal and, more especially, choroidal inflammation is an interesting one; whether the cause is a retinitis or a choroiditis, one would expect in Coats' disease always to find evidence of the response of the epithelium to such localized intoxication. Marshall and Michaelson, however, showed that in their five cases the epithelium was uninterrupted throughout. This is difficult to explain, especially as the number of bladder cells present was greater than has been reported by any other worker, certainly much greater than in the cases depicted by Coats. Moreover, none of their cases showed any vascular anomaly, nor was there inflammation of the choroid; it seems to us, in fact, that the evidence that the bladder cells had an inflammatory origin is not great. There is more to support the view that the lesion these workers described was a primary lipoidal degeneration of the retinal pigment epithelium. It is, at any rate, a possibility to be kept in mind. As for the present case, it seems straightforward; there is no doubt that we are dealing with a choroiditis which has produced marked subretinal exudation and, as a result, a big detachment. Von Hippel (1913) suggested that the vascular changes and hemorrhages found in Coats' disease follow this sort of thing; it appears highly probable that this is what has happened in the case reported here. The development of bladder cells in such circumstances is not surprising, although the restriction of their places of origin to those areas we designate as colloid bodies is an unusual feature, suggesting how the origin of these cells from the retinal pigment layer might be missed.

Summary

A case classified as a pseudoglioma, bilateral and advanced, was diagnosed with the aid of a biopsy through the posterior eye as probably one of Coats' disease. Subsequent microscopic examination of the whole eye confirmed that it was not a glioma and strongly supported the diagnosis of Coats' disease. The microscopic appearance suggested that the original condition had been an exudative choroiditis.

The development of the fatty granular cells which characterize disease of this type could be traced from small localized areas of proliferating retinal pigment cells at different points along the retina. Immediately underlying these colloid-like bodies, the choroid was infiltrated with chronic inflammatory cells. While the entire pigment epithelium was affected, clumping of the cells having occurred throughout its length, it was only at these localized sites that mutation from a fixed pigment epithelial cell to a free depigmented fat phagocyte seemed to occur.

Gandhi Eye Hospital.

REFERENCES

1. Coats, G.: Roy. Lond. Ophth. Hosp. Rep. 18: 440, 1908.

2. Leber, T. K.: in Handbuch der gesamten Augenheilkunde, edited by von Graefe, A. C., and Saemisch, T., Leipzig, W. Engelmann, Vol. 7, 1915, p. 1267.

3. Marshall, J., and Michaelson, I. C.: Tr. Ophth. Soc. U. Kingdom 53:102, 1933.

4. von Hippel, E.: Arch. Ophth. 86:443, 1913.

5. Wolff, E.: A Pathology of the Eye, Ed. 3, London, H. K. Lewis & Co., Ltd., 1951, p. 163.

The Electromyography of Vergence Movement

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In a previous report[1] a difference was described between the electromyographic pattern of version and convergence movement. The version, or saccadic, movement was shown to be associated with a sudden short discharge of larger motor units immediately followed by a regular pattern of lower amplitude. Corrective secondary bursts are often introduced upon this consistent discharge. Convergence is accompanied by a gradual increment of motor units and succeeded by a prolonged decrement. Alterations in the firing rate are slow in nature, and secondary adjustments are not seen. More recent data has shown that the two patterns are often combined in certain vergence movements and that more subtle changes are found in the motor units.

Differences of opinion have been expressed as to the findings in asymmetric convergence. One group[2] has found coactivity of the medial and lateral rectus of the stationary eye, while another[3,4] described no alterations. It is hoped that the present study will help to resolve some of the diversity of views about asymmetric convergence.

Submitted for publication May 6, 1959.

From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine.

Presented in part at the Midwestern Section of the Association for Research in Ophthalmology, Denver, April 18, 1959.

This investigation was supported in part by Research Grant B-1349 from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

I. Method

The subject was fixed in a headrest and a wax bite-bar to prevent head movement. A fixation light was placed 18 ft. in front, and a stimulus light was placed at intervals of 2.5 to 25 degrees to the side for version movement. Convergence was obtained by a clear Plexiglas plate placed in front of the subject with a 1 mm. diameter defect drilled in the center. The plate was illuminated from the side and was adjustable so that both sudden symmetrical and asymmetrical convergence of 2.5 to 25 degrees were produced. Gradual convergence could be produced by slowly approximating this object.

Recordings were obtained from six normal persons, 24 to 43 years of age. The recording apparatus was that previously described. The medial and lateral rectus of one eye was used at the initiation of the procedure. After obtaining pertinent data, one electrode was removed, since it was noted that the insertion of multiple electrodes produced erratic eye movements, particularly if they are maintained for over 30 minutes.

II. Results

A. Convergence.—After the introduction of the stimulus at the beginning of the lateral rectus tracing of Figure 1, there is a

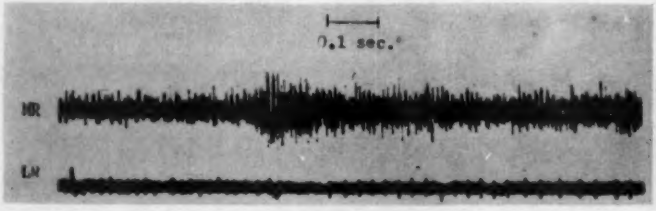


Fig. 1.—Ten degrees convergence.

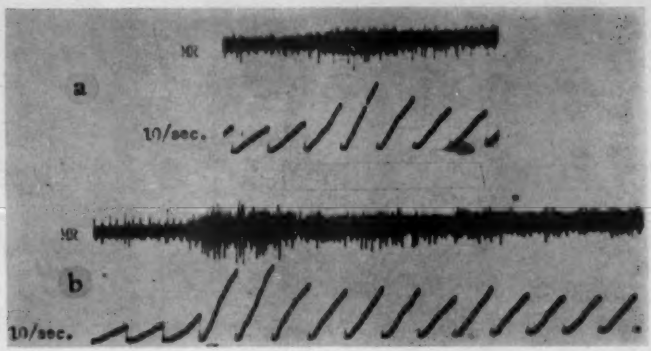


Fig. 2.—(*a*) Five degrees convergence; (*b*) twenty-five degrees convergence.

latent period of 0.4 seconds. This is followed by an increase in the activity of the medial rectus for 0.06 seconds. Maximal activity is maintained for 0.1 seconds, and then there is a gradual decline. The lateral rectus single unit pattern shows reciprocity throughout, with complete inhibition during the height of activity in the internal rectus. over 0.2 seconds and then a gradual decline for 0.8 seconds. In smaller movements differences are noted for a shorter time but usually require at least 0.4 seconds before stability is reached. Single motor unit (Fig. 3) discharge follows the general pattern with increasing frequency of firing at the onset followed by a more gradual decrease.

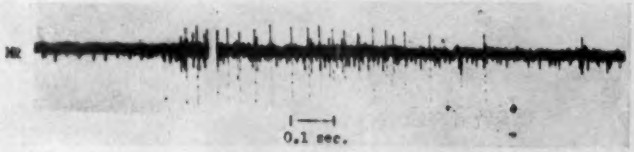
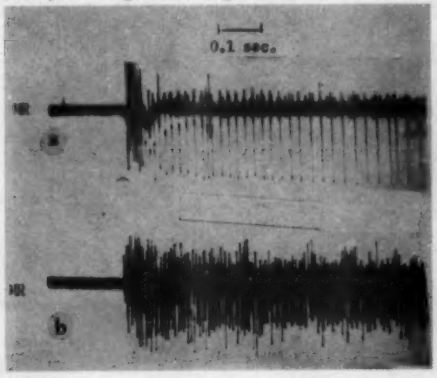


Fig. 3.—Five degrees convergence.

Figure 2 illustrates the gradual alterations of myography in convergence by integration at 10 per second. In a large movement there is increasing activity for

Fig. 4.—(*a*) Twenty-five degree saccadic; (*b*) twenty-five degree convergence.



Upon comparison of the motor unit activity between saccadic and convergence activity (Fig. 4), it is noted that convergence has more motor units present and at least some of the units are different, with use of amplitude as the distinguishing criteria.

B. Divergence.—The electromyography of divergence was found to consist of two types. The first form (Fig. 5) demonstrates coactivity of the medial and lateral rectus. The medial rectus shows slightly diminishing activity up to a saccadic burst and then the presence of a uniform firing pattern. The lateral rectus recording has the spindle-shaped pattern that was seen in the recordings of the medial rectus for convergence, and the first increase in activity occurs with the beginning of the saccadic burst in the medial rectus.

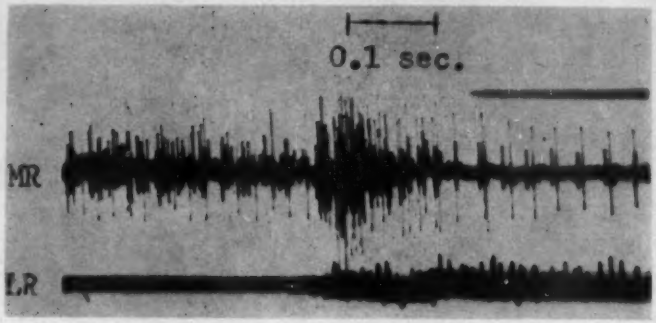
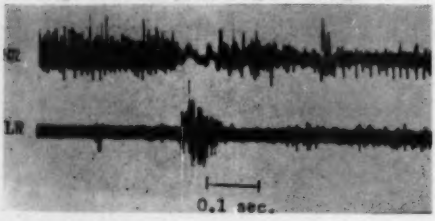


Fig. 5.—Divergence from 20 degrees.

The second form (Fig. 6) is marked by inhibition of the medial rectus (0.1 second) with the reappearance of an irregular pattern (0.25 second) followed by a steady-firing state of fixation. Accompanying the inhibition of the internus, there is a saccade in the lateral and an irregular pattern that reciprocates with the medial until a stable state is reached.

Fig. 6.—Twenty-five degree divergence.



Divergence also has the secondary bursts of saccadic movement. Figure 7 illustrates the motor unit pattern, as well as the secondary adjustments that occur in a serial fashion.

C. Asymmetric Convergence.—Sudden asymmetrical convergence is characterized by a saccadic burst in yoke muscles followed by a convergence pattern in the medial recti. This is shown in Figure 8 for the adducting eye. The supposedly stationary eye shows similar changes, except that the saccade occurs in the lateral rectus and is then followed by a convergence pattern in the medial rectus.

If the subject is required to follow a slowly moving target that approaches one eye from straight ahead, no alteration in the electromyography is noted until the object approaches the near point of convergence when coactivity begins (Fig. 9). The lateral rectus trace indicates the single motor unit pattern as it increases concomitant with the medial rectus (6 cm.). Further activity is seen as the break point of convergence is approached (3 cm.). Divergence occurs in one of the two forms previously described. A recording from a medial rectus (Fig. 10)

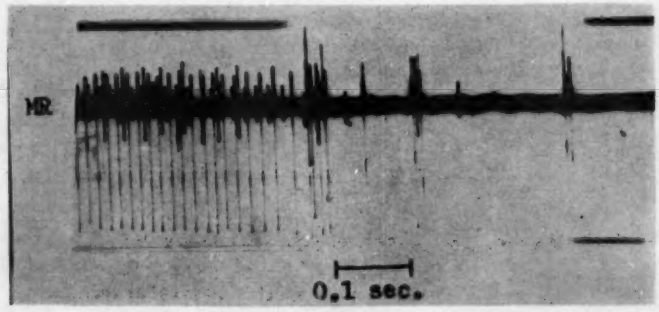


Fig. 7.—Ten degree divergence.

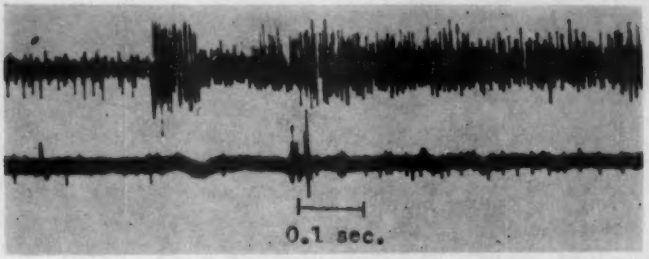


Fig. 8.—Asymmetric convergence.

indicates that no alteration in single motor units is noted until a distance of 6 cm. and further activity occurs up to divergence.

seem to require corrective adjustments. The motor units that are involved in the movement show similar changes in their rate of

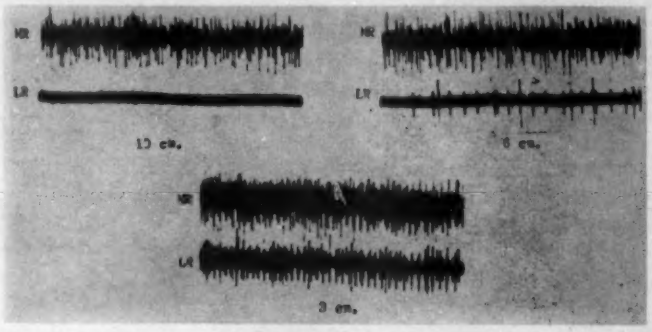


Fig. 9.—Asymmetric convergence.

III. Comment

Convergence movement has many features that distinguish it myographically from saccadic eye movement. The onset has a more gradual increment, and after the initial rise there is changing activity for almost a second. The activity is of a regular fashion with slow changes which do not discharge. In addition, there are more units present in convergence motion and at least some of the units are different. Once fixation is obtained in convergence, a different pattern is also still present.

The first form of divergence shows features of both convergence and saccadic movement. There is coactivity of the medial

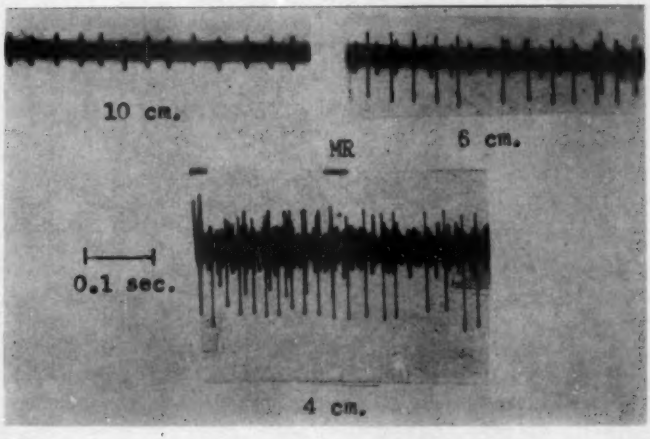


Fig. 10. — Asymmetric convergence.

and lateral rectus, with a saccade occurring in the medial; concomitantly the spindle pattern is seen in the lateral rectus. The second form of divergence consists almost entirely of saccadic elements with bursts being seen in both medial and lateral recti, and often what are apparently corrective adjustments are observed. There is no doubt that divergence is active. It is possible that the two forms of divergence may be on a sampling basis, since only a small area of an ocular muscle is surveyed at one given interval with an electrode and one form of activity may be missed.

Sudden asymmetric convergence has been described [5,6] as consisting of a version movement to the side of the object, followed by convergence of both eyes. The electromyographic pattern shows similar findings with the convergence pattern following after the saccadic pattern. The delay between the convergence and version pattern is about equal to the latent period for the movement.

If a subject slowly approximates an object approaching directly in front of one eye, there is no increase in coactivity of horizontal antagonists until the near point of convergence is approached. From this point until divergence an increase of simultaneous activity is seen. Single motor units are useful in this observation, since changes in fixation as small as 2 degrees 30 minutes can be discerned.[1]

In view of coactivity as a normal variant of divergence, it would seem that this phenomenon is the beginning of divergence under the conditions of a slowly advancing stimulus. As support for this hypothesis is the finding of coactivity in normal subjects at the near point of symmetric convergence. Furthermore, in subjects with a remote near point of convergence, this simultaneous increase is seen at a greater distance for both symmetric and asymmetric convergence.

IV. Conclusions

1. Convergence utilizes more motor units than saccadic movement of the same magnitude.

2. Part of the motor units are different in the two patterns.

3. Divergence activity resembles saccadic movement, and the pattern is different from convergent motion.

4. Sudden asymmetric convergence is accompanied by a saccadic burst in agonists, followed by a convergent pattern in both medial recti.

5. No increase in coactivity of horizontal antagonists is noted with slow asymmetric convergence on an approaching target until the near point of convergence is approached.

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REFERENCES

1. Miller, J. E.: Electromyographic Pattern of Saccadic Eye Movements, Am. J. Ophth. 46:183, 1958.

2. Tamler, E.; Jampolsky, A., and Marg, E.: An Electromyographic Study of Asymmetric Convergence, Am. J. Ophth. 46:174, 1958.

3. Breinin, G. M.: The Nature of Vergence Revealed by Electromyography, A. M. A. Arch. Ophth. 54:407, 1955.

4. Blodi, F. C., and Van Allen, M. W.: Electromyography of Extraocular Muscles in Fusional Movements: I. Electrical Phenomena at the Breakpoint of Fusion, Am. J. Ophth. 44:136, 1957.

5. Dodge, R.: Five Types of Eye Movements in the Horizontal Meridian Plane of the Field of Regard, Am. J. Physiol. 8:307, 1902.

6. Westheimer, G., and Mitchell, A. M.: Eye Movement Responses to Convergence Stimuli, A. M. A. Arch. Ophth. 55:848, 1956.

Electroretinographic Measurement of the Spectral Sensitivity in Albinos, Caucasians, and Negroes

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The albino's pupil appears red when the eye is diffusely illuminated, but when no light is transmitted through the iris and sclera the pupil appears black.[1] The degree of fundus pigmentation is important not only when there is diascleral exposure, but also when all of the light enters the eye through the pupil, since light diffusely reflected from the fundus indirectly stimulates a wide area of photoreceptors.

It has been shown by measurement of the electroretinographic threshold in albino rabbits that the effect of scattered light from the red end of the spectrum far exceeds that from the blue end, and thereby greatly modifies the shape of the electroretinographic spectral sensitivity curve.[2,3] The purpose of this investigation was to extend such observations to include a study of the influence of varying amounts of retinal pigmentation in humans. This seems especially desirable since the method of cone electroretinography with spectral stimuli can be used in diagnosing and studying color defectives.[4,5]

Materials and Methods

Subjects were chosen who showed varying degrees of retinal pigmentation. Five types of fundi were distinguished as follows: albino, fair (blond) and dark Caucasians, and light and dark Negroes. The albino fundus appears light orange-pink in color, and the choroidal vessels are seen with great clarity. In eight of the nine albinos examined, there was slight pigmentation in the macular area which partially obscured the choroidal vessels in this region. All subjects exhibited complete or incomplete universal albinism, a coarse horizontal nystagmus, and absence of foveal reflexes. For a more complete description of the ocular findings in albinos and their symptoms see Falls, 1953.[6]

The blond or fair Caucasian fundus appears predominantly light pink, but slightly darker than that of the albino, and although some choroidal vessels are visible, they are not as apparent as in the albino and, unlike the latter, foveal reflexes are present. Three subjects with blond fundi were examined.

Four Caucasians with relatively densely pigmented fundi, three Negroes with dark fundi, and five Negroes with even more darkly pigmented fundi were also studied. In the majority of patients there was a good correlation between the color of the fundus (light red, dark red, chocolate-colored, slate-gray) and the depth of general skin and hair pigmentation. None of the individuals tested showed any deficiency of color vision when tested with the Hardy-Rand-Rittler pseudoisochromatic plates or the Farnsworth panel D-15 color discs.

The method of stimulation, recording, and measurement of the relative spectral sensitivity curves has been described previously.[4] In the albinos, a quantitative evaluation of the experimental data was possible only in those cases in which the frequency of the nystagmus was so low as not to interfere with the recording of the electroretinal flicker (32 per second) potentials. Because

Submitted for publication June 1, 1959.

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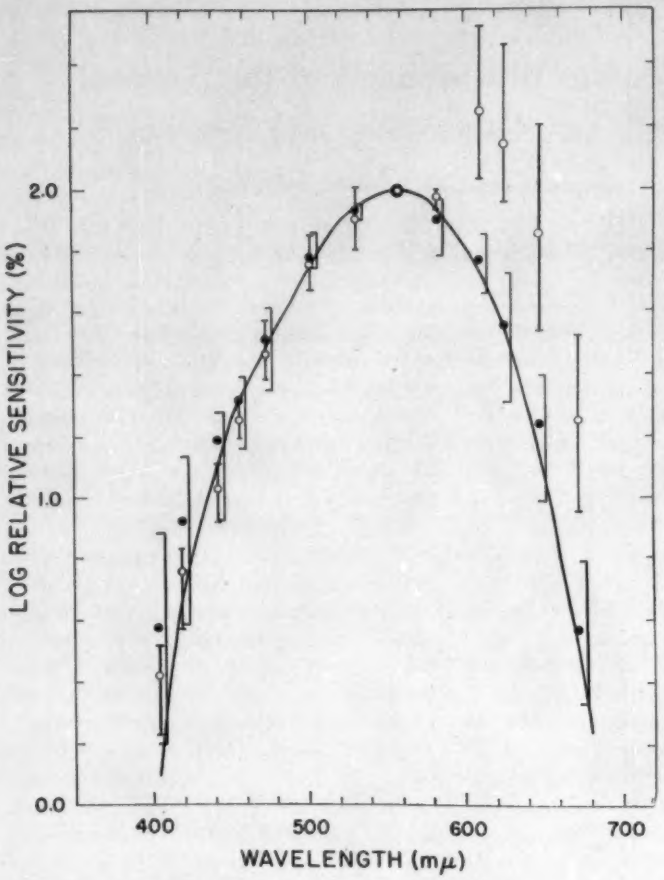

Fig. 1.—Comparison of electroretinographic and psychophysical sensitivity curves. Relative spectral sensitivity of dark-pigmented eyes (four "dark" whites, three "light" Negroes, filled circles) and six albinos (open circles), obtained by measurement of the energy required for constant amplitudes of photopic (32 per second) potentials for an equal-energy spectrum from wavelengths 404mμ-672mμ. Small-area retinal stimulation was used. Dots and circles-averages, vertical lines-extreme values. Solid line-Wald's (1945) psychophysical cone sensitivity determinations eight degrees from the fovea.

of the nystagmus, the electroretinographic findings in three of the albinos could only be qualitatively evaluated. In the other albinos, repeated examinations at different sessions were made. On several occasions the nystagmus was sufficiently reduced so that data could be obtained not only with stimulation by parallel light (small area of retinal stimulation), but also with a Maxwellian view (large area of retinal stimulation).

In several subjects (1 albino, 1 blond, and 2 dark Caucasians) the flicker electroretinogram was recorded using diascleral illumination and the results compared with those obtained in the same subject with the light entering through the pupil. In these experiments a strong convex lens was used to focus the light beam on the sclera about 5 mm. from the limbus.

Results

1. *Spectral Sensitivity in Subjects with Different Degrees of Retinal Pigmentation.*

In Figure 1, the average relative spectral sensitivity of six albinos (open circles) determined by flicker electroretinography with small-area retinal stimulation is compared with corresponding values from darkly pigmented fundi (filled circles). While the sensitivity of the latter agrees well with the psychophysical cone (8 degrees from the fovea) sensitivity curve (solid lines) ob-

tained by Wald,[7] the corresponding values in albinos are appreciably higher at longer wavelengths. The maximum sensitivity among the available wavelengths was at 558mμ in the normally pigmented eyes, but was shifted to 610 mμ in albinos. In the latter, the highest relative sensitivity recorded at 610 mμ was 340% (for still higher values cf. Fig. 4*A*), while the lowest was 110% (with 558mμ arbitrarily adjusted to equal 100%).

It is apparent that not only do the spectral sensitivity curves differ in albinos where there are important defects in retinal function in addition to the generalized absence of pigmentation, but also in individuals with normal retinal function where the only difference is in the degree of fundus pigmentation. In Figure 2, Negroes (filled circles) show a distinctly lower sensitivity than Caucasians with lighter fundi (open circles) at wavelengths longer than 600mμ. A comparison of the sensitivity curves in relation to the degree of fundus pigmentation yields a clear sequence of increased sensitivity in the long wavelength part of the spectrum with decreasing (fundus) pigmentation, while no similar changes occur at shorter wavelengths (Fig. 3).

2. *The Influence of Stimulus Area and Intensity on the Spectral Sensitivity of Albinos.*—Previous work on rabbits has shown that the electroretinographic spectral sensitivity curve of the albino departs significantly from that obtained in pigmented animals. The former show predominantly narrower curves with a definite hump in the red. When the spectral sensitivity curve of the

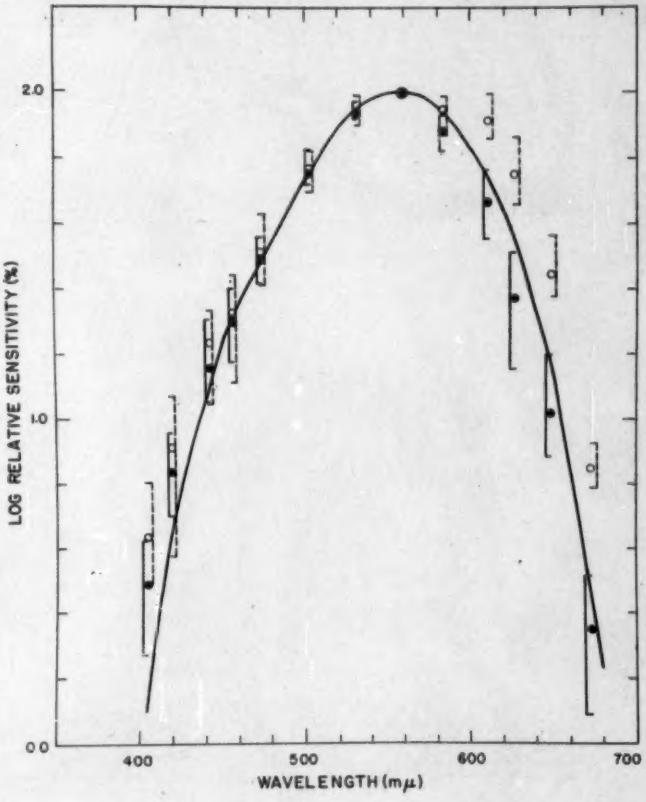

Fig. 2.—Comparison of electroretinographic and psychophysical sensitivity curves. Relative spectral sensitivity of six lightly pigmented Caucasians (open circles) and five darkly pigmented Negroes (filled circles) obtained by measurement of the energy required for constant amplitudes of photopic potentials (32 per second) for an equal-energy spectrum with wavelengths 404mμ-672mμ. Small-area retinal stimulation was used. Dots and circles-average values, vertical lines-extreme values. Solid line-Wald's (1945) sensitivity of peripheral (8 degrees from fovea) cones.

pigmented rabbit is subtracted from the spectral sensitivity curve of the albino, the difference can be explained qualitatively in terms of the spectral reflection of blood measured in vitro.[2] Further experiments in the albino rabbit have shown that in addition to the area directly illuminated other retinal areas are illuminated indirectly by light diffusely reflected from the fundus. When the entire retina is illuminated, the difference in sensitivity between the pigmented and albino animals is very small.[3]

From the findings in the preceding section, it may be assumed that the increased red sensitivity in humans with decreasing fundus pigmentation may have an explanation similar to that in rabbits. However, it is difficult in human subjects to reduplicate the experimental conditions to provide as critical an analysis as is possible in animal studies. Nevertheless, even in man the area of retinal illumination may be increased sufficiently to reduce the influence of reflected light.

Figure 4 shows the sensitivity curves from two separate experiments on the albino with stimulation of a small (*A*) and larger retinal area (*B*). It is obvious that the shape of the relative spectral sensitivity curve depends not only on the size of the retinal area stimulated, but also on the potential criterion upon which the calculations of the sensitivity curves were based. Thus, regardless of stimulus area, as the stimulus strength increases (higher criteria) there is a relatively greater increase in potential for wavelengths between 583mμ and 672mμ than at shorter wavelengths.

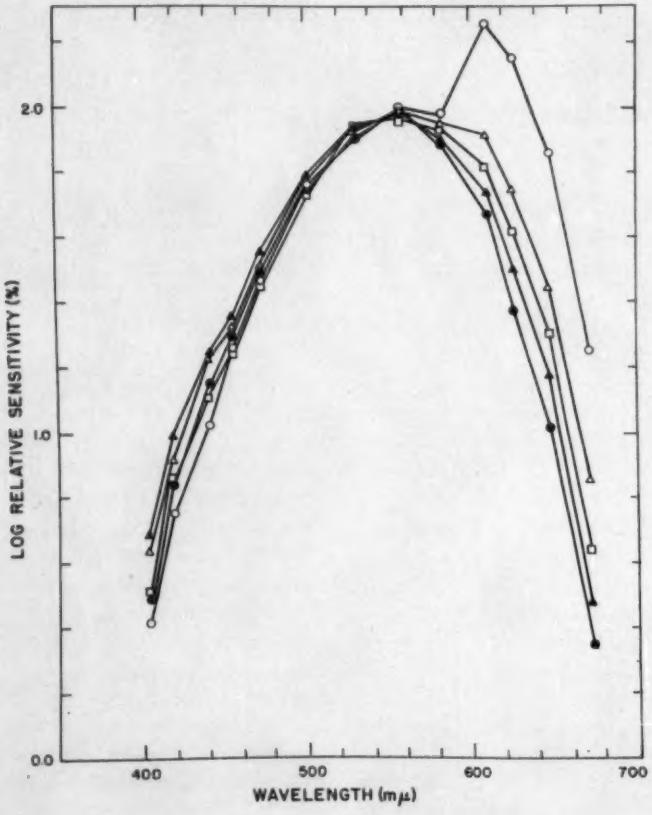

Fig. 3.—Relative spectral sensitivity with different fundus pigmentation, obtained by the measurement of the energy required for constant amplitudes of photopic flicker potentials (32 per second) for an equal-energy spectrum with wavelengths 404mμ-672mμ. Small-area retinal stimulation was used. Dots-average of "dark" Negroes. Solid triangles-average of "light" Negroes. Open squares-average of darkly pigmented Caucasians. Open triangles-average of lightly pigmented Caucasians. Circles-average of albinos.

However, the sensitivity changes for different intensities with small and large areas of retinal stimulation are quite different. For example, with a small area of retinal stimulation the sensitivities calculated for 610mμ (sensitivity at 558mμ=100%) are 200% for 31μV, 300% for 50μV, and 500% for 75μV (Fig. 4*A*), while with a larger stimulus area the sensitivity at 610mμ is 51% at 37μV, 135% at 61μV, and 285% at 105μV (Fig. 4*B*). The higher blue sensitivity in albinos shown here for larger stimulus areas has been described previously for subjects with pigmented fundi.[4] The lower red sensitivity in the albino with the large-area stimulation is easily explained if one assumes that the relative contribution of light from indirect illumination is reduced by increasing the area of direct stimulation. It is more difficult to understand the increase in red sensitivity with increasing stimulus strength, because in this case the area directly illuminated becomes larger through Tyndall scatter produced by the ocular media.[4] However, since the scattering effect of the media must be similar in pigmented and albino eyes, a different explanation must be sought. It is suggested that part of the light diffusely reflected from the fundus becomes suprathreshold only with higher intensity stimuli.

3. *Differential Absorption of Spectral Light Entering the Eye Through the Sclera.* If it is considered that the albino fundus in man is not completely devoid of pigment, the agreement between the differences in sensitivity between albino and pigmented human eyes (Fig. 5 right, solid line) and the corresponding values in rabbits (open circles, Dodt & Walther[2]) seems satisfac-

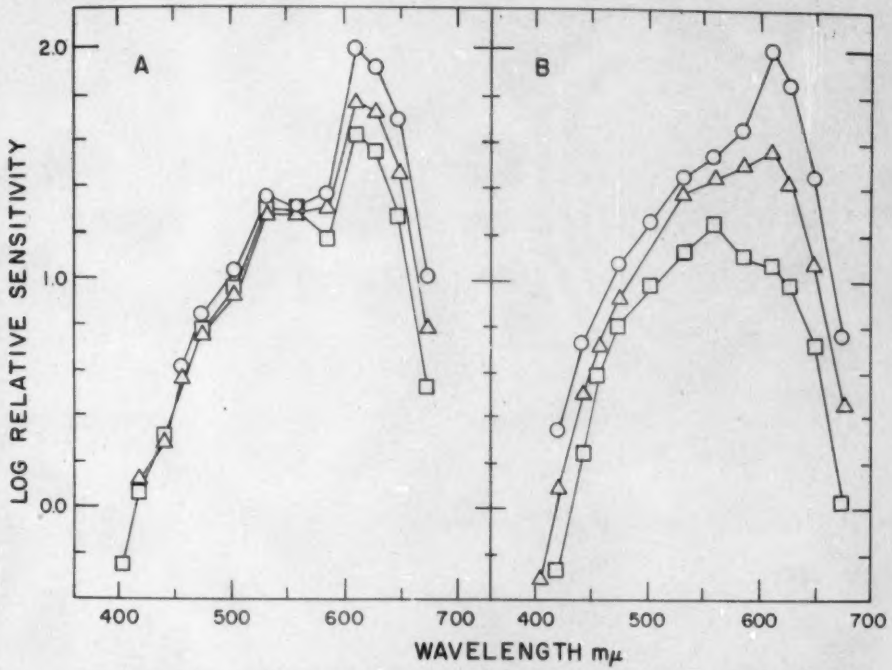

Fig. 4.—Relative spectral sensitivity of two albinos with stimulation of a small (*A*) and larger (*B*) area of the retina, obtained by measurement of the energy required for constant amplitudes of photopic flicker potentials (32 per second) for an equal-energy spectrum with wavelengths 404mμ-672mμ. Potential levels (*A*): 31μv-squares, 50μv-triangles, 75μv-circles. Potential levels (*B*): 37μv-squares, 61μv-triangles, 105μv-circles. The location of the curves along the ordinate is arbitrary.

tory. Since Dodt and Walther have shown that the difference is sensitivity between pigmented and albino rabbits can be explained in terms of the spectral reflection of blood, it can be assumed that the changes in spectral sensitivity observed in human albinos are similarly caused by the absence of pigment in the epithelium.

The measurements of blood pigment in the living eye are of interest for general reasons as well as for an understanding of the physiology of light perception in the human albino. Therefore, the experiments were extended to include the results of diascleral illumination.

The results so obtained were handled in the same way as for the previous experiments and the energy values were again expressed in relative sensitivities. The expected difference in the electroretinographic threshold was observed between normally pigmented and albino human eyes with

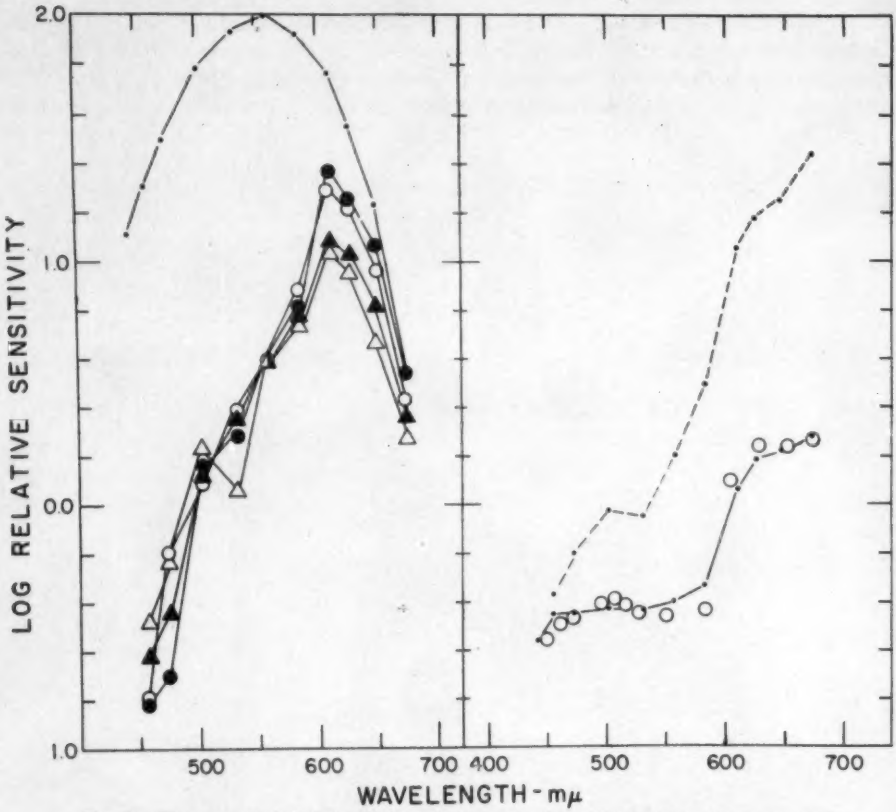

Fig. 5.—Shown on the left below is the relative spectral sensitivity obtained by measurement of the energy required for constant amplitudes of photopic flicker potentials with diascleral illumination with an equal-energy spectrum with wavelengths 456mμ-672mμ. Open circles-albino, open triangles-blond fundus; solid triangles and solid circles-2 darkly pigmented Caucasians. Above, on the left, is the relative spectral sensitivity of darkly pigmented eyes with illumination through the pupil (from Fig. 1). On the right, the dash line represents the relative difference between the spectral sensitivity with stimulation through the pupil and through the sclera. The solid line represents the relative difference between the spectral sensitivity of dark-pigmented and albinotic fundi with illumination through the pupil (from Fig. 1). The open circles on the right show the relative difference, reduced in scale, between the spectral sensitivity of pigmented and albino rabbits (Dodt and Walther, 1958).

diascleral illumination. In Negroes the potentials were so small, even at the long wavelengths, that it was impossible to make a quantitative evaluation of the data. In darkly pigmented Caucasian eyes the relative sensitivity could be calculated between 672mμ and 456mμ, but at still shorter wavelengths the measurements became increasingly more difficult even for albinos. The most obvious result of these experiments is the close agreement of all relative spectral sensitivity curves regardless of the degree of retinal and choroidal pigmentation (Fig. 5, left). Accordingly, it can be assumed that none of these eyes contain any great concentration of selectively absorbing pigment. Thus, if hemoglobin is the only selectively absorbing pigment filter for the light passing through the eye wall, the difference in spectral sensitivity produced with pupillary (Fig. 5, upper left) and diascleral illumination (circles and triangles) could be expected to reflect the transmission spectrum of oxyhemoglobin. In Figure 5 right, the dash line shows this difference, while the solid line represents the spectral reflectivity curve of hemoglobin determined electroretinographically in humans compared with that obtained in rabbits (circles) found by Dodt and Walther.[2]

Since the human choroid is variable in thickness, it is not possible to make any exact calculations of the blood content from differences in spectral sensitivity found in this study. However, even the roughest calculations indicate a blood content which is much too high, especially since the sclera is relatively avascular. Dodt and Walther[3] found a similar discrepancy in experiments on rabbits which was investigated in detail. They ascribe this discrepancy to selective scattering of light and the dependence of the electroretinographic threshold on the area of retinal stimulation.

Comment

The electroretinographic threshold of the human eye is directly related to the light intensity, and reciprocally to the size of the retinal area exposed.[8] The present investigation emphasizes the importance of the size of the retinal area stimulated in regard to its influence on the measurement of spectral sensitivity. When only a small retinal area is directly stimulated, diffuse reflection from the fundus produces an indirect stimulation of additional retinal area which is more pronounced for some wavelengths. For example, in eyes which are functionally normal and vary only in their pigmentation, small-area stimulation at 610mμ shows a relative sensitivity of 47% in the Negro, 60% in the dark Caucasian, and 83% in the light Caucasian (sensitivity at 558mμ is equated at 100% in all cases). If the electroretinographic measurements are to be compared to visual pigment absorption, it appears desirable from these experiments to use wide-area retinal illumination which can be achieved by using a contact lens with a diffusing corneal surface as described by Heck.[9]

Evidence of defective color vision in albinos[10,11] cannot be deduced from the findings reported. The sensitivity curves of albinos (Fig. 6, open circles) and of protanopes (filled triangles) showed opposite deviations on the red side of the spectrum from the normal (filled circles). It should be emphasized that the increased red values found for the albino do not imply an increase in red sensitivity of the retina itself, since the albino sensitivity curve returns to normal when low intensity, large-area retinal stimuli are used. No such changes occur in the sensitivity curve of the protanope.[6] Also, the relative spectral sensitivity in protanopes begins to deviate from the normal at wavelengths longer than 502mμ, while the sensitivity variation in albinos occurred only above 583mμ (Fig. 6).

Although the albino may have no alteration in the spectral sensitivity of its photoreceptors, his color vision may actually be significantly changed by simple reflection of light from his red fundus.

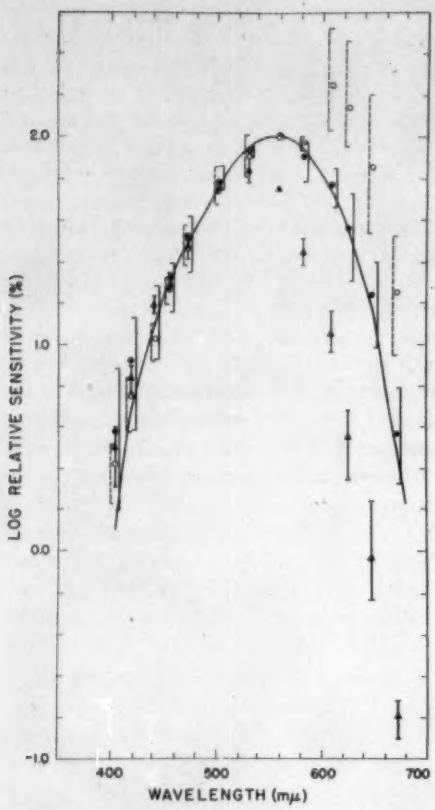

Fig. 6.—Relative spectral sensitivity of darkly pigmented Caucasians (filled circles), and albinos (open circles), compared with the values obtained in protanopes (solid triangles) from Dodt, Copenhaver, and Gunkel, 1958. The solid line is Wald's (1945) sensitivity of peripheral (8 degrees from fovea) cones.

Summary

The relative spectral sensitivity of the photopic component of the electroretinogram was measured in human albinos, Caucasians, and Negroes. Wavelengths between 404mμ and 672mμ were studied using flickering stimuli at a frequency of 32 per second.

Direct stimulation of small retinal areas, which included the fovea and some adjacent retina, showed the relative sensitivities for wavelengths longer than 583mμ to be low in Negroes and high in albinos, while light Negroes, dark Caucasians, and subjects with "blond" fundi showed intermediate sensitivities. The maximum sensitivity in albinos occurred at 610mμ as compared with a peak sensitivity at 558mμ for Caucasians and Negroes. The difference in spectral sensitivity between deeply pigmented and albino eyes was similar to the spectral reflection of blood.

The sensitivity peak of 610mμ in albinos was most prominent for small-area intense stimuli. With larger stimulus areas and weaker stimuli the albino sensitivity in the red is decreased to almost normal values. It is concluded that the increased red sensitivity in albinos is caused by scattered light which is diffusely reflected from the fundus.

Indirect retinal stimulation through the sclera and choroid was used to evaluate the relative spectral transmission by pigment in the outer coats of the eye. By this method little difference was found between the relative spectral sensitivity curves of subjects with albino, blond, and deeply-pigmented Caucasian fundi. It is therefore concluded that the only selective absorption of light in the wall of the eye is due to oxyhemoglobin. Neither the blood volume nor the pigmentation in the outer coats of the eye can be quantitatively assessed by this method because of uncertainties in the retinal area stimulated due to scattering of light.

We wish to thank Dr. Katharine Tansley and Dr. J. B. Walther for their criticism and suggestions, and Dr. Carl Witkop for obtaining the albino subjects used in this study.

Ophthalmology Branch, National Institutes of Health (14).

REFERENCES

1. Donders, F. C.: Verbetringen van den Oogsspiegal; Onderzoekingen gedan in het physiologisch Laboratorium der Ulrechtsche Hoogschool, Jaar VI:153, 1854.

2. Dodt, E., and Walther, J. B.: Spektrale Sensitivität und Blutreflextion; Vergleichende Untersuchungen an pigmentierten und albinotischen Netzhäuten, Pflüger's Arch. ges. Physiol. 266:187-192, 1958.

3. Dodt, E., and Walther, J. B.: Elektroretinographische Messung der Spektralsensitivatät

von Albinoaugen bei direkter und diaskleraler Belichtung, Pflüger's Arch. ges. Physiol. 268:435-443, 1959.

4. Dodt, E.; Copenhaver, R. M.; and Gunkel, R. D.: Photopischer Dominator und Farbkomponenten in menschlichen Elektroretinogramm, Pflüger's Arch. ges. Physiol. 267:497-507, 1958.

5. Copenhaver, R. M., and Gunkel, R. D.: The Spectral Sensitivity of Color Defective Individuals Determined by Electroretinography, A.M.A. Arch. Ophth. 62:55-68, 1959.

6. Falls, Harold: Albinism, Tr. Am. Acad. Ophth. 57:324-331, 1953.

7. Wald, G.: Human Vision and the Spectrum, Science, 101:653-658, 1945.

8. Crampton, G. H., and Armington, J. C.: Area-Intensity Relation and Retinal Location in the Human Electroretinogram, Am. J. Physiol., 181: 47-53, 1955.

9. Heck, J.: The Flicker Electroretinogram of the Human Eye, Acta physiol. scand., 39:158-166, 1957.

10. Pickford, R. N.: Color Vision of an Albino, Nature, London 168:954, 1951.

11. Pickford, R. N.: Color Vision of Three Albinos, Nature, London 131:361-362, 1958.

Electromyographic Study of Following Movements of the Eye Between Tertiary Positions

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In a previous paper,[1] coactivity of extraocular muscles was studied during slow following movements with utilization of multiple channel electromyography. After this, a study of coactivity during following movements of the eye between tertiary positions was attempted. The same technique, previously described,[2] was employed.

Cocontraction is defined as a simultaneous increased contraction of extraocular muscles which are normally antagonistic in their primary field of action. By movements between tertiary positions, we mean horizontal movements in upper and lower fields of gaze and vertical movements in right and left fields of gaze. We shall sometimes refer to the planes of such movements as tertiary planes.

The upper and lower fields of gaze were approximately 40 degrees above and below the horizontal. The right and left planes of gaze were approximately 50 degrees to either side of the primary position. Similarly, the amplitudes of the vertical movements were approximately 40 degrees above and below the horizontal, while the horizontal excursions were approximately 50 degrees to either side. The target consisted of a small light held at a distance of about 70 cm. from the eye. All electromyograms in this paper were filmed at a camera sweep speed of 30 in. per minute.

It became apparent early in this experiment that we could not look for coactivity in tertiary plane movements, because in each field of gaze one member of the pair of muscles to be observed for coactivity was largely inhibited and any small changes in its activity would not be visible on the tracing. However, these movements yielded other interesting information, and it is the purpose of this paper to report such findings.

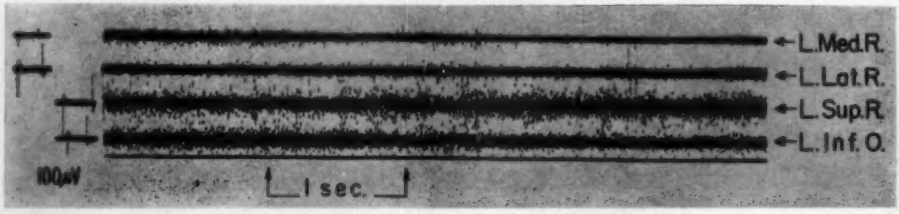
Submitted for publication May 1, 1959.

From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine, San Francisco. This study was supported by funds made available under the Office of Naval Research Contract Nonr 225(20) and U. S. Public Health Service Grant B 686. School of Optometry, University of California, Berkeley (Dr. Marg).

A. Horizontal Movements in Upper Field of Gaze

Here it appears that the superior and inferior rectus muscles are more active in abduction, whereas the inferior oblique was more active in adduction. No insertions

Fig. 1.—Left eye moving from up and right to up and left gaze. Note increased activity of left superior rectus in abduction and left inferior oblique in adduction.



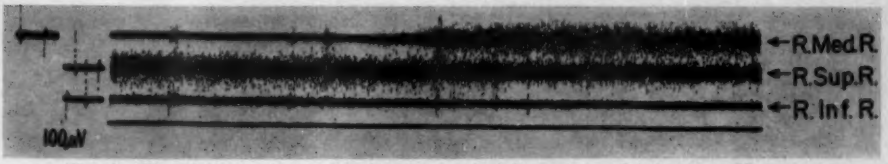


Fig. 2.—The right eye is moving from up and right to up and left gaze. Note greater right superior rectus activity in abducted position and no change in the inhibited right inferior rectus.

were made into the superior oblique through the intact conjunctiva, and, therefore, no recordings of this muscle will be shown.

In Figure 1 the left eye is moving from the up and right field of gaze to the up and left field of gaze. Note that as the eye undergoes this movement the left superior rectus increases in electrical activity, while the left inferior oblique decreases in activity. This finding of increased electrical activity of the vertical recti in abduction and the inferior oblique in adduction was very constant within and among subjects.

Again, in Figure 2, as the right eye moves from up and right position to up and left gaze, the right superior rectus shows greater electrical activity in the abducted position as compared with the adducted position. The right inferior rectus, inhibited in the upper field of gaze, shows no significant change in electrical activity.

B. Horizontal Movements in Lower Field of Gaze

Here again the vertical recti show greater activity in abduction and the inferior oblique is most active in adduction.

In Figure 3*A* the right eye is in the down and right position. In Figure 3*B*, taken a moment later, the same right eye has moved to the down and left position. Note the greater activity of the right inferior rectus in the abducted as compared with the adducted position. The superior rectus, inhibited in down gaze, shows no change, while the horizontal recti show the appropriate change of reciprocal innervation.

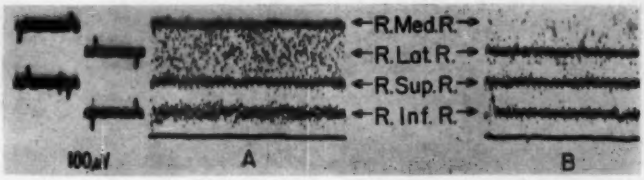


Fig. 3.—In *A* the right eye is in down and right gaze; in *B* the same eye, a moment later, in down and left gaze. Note greater right inferior rectus activity in abducted position and no change in the inhibited right superior rectus.

Figure 4 also demonstrates increasing activity of the right inferior rectus as the right eye moves from down and left gaze to down and right gaze. Again, there is no observable change in the inhibited superior

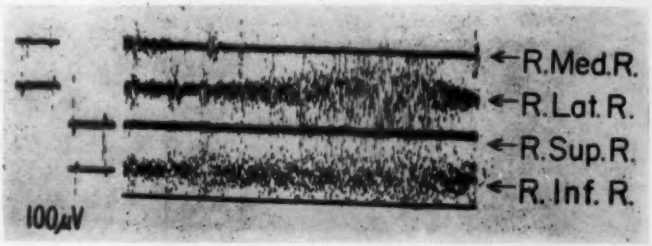


Fig. 4.—Right eye moving from down and left to down and right gaze. Note greater right inferior rectus activity in abduction and no change in the inhibited right superior rectus.

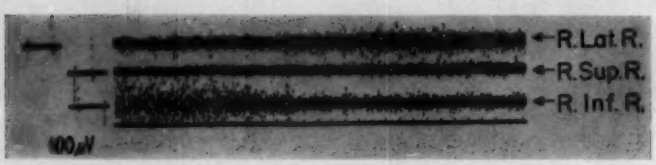


Fig. 5.—The right eye is moving from down and right to up and right gaze. Note increased right lateral rectus activity in the upper field of gaze.

rectus muscle, while the horizontal recti show the expected reciprocal innervation.

C. Vertical Movements in the Right Field of Gaze

In contrast to the findings above, the horizontal recti show great variability of activity from subject to subject in vertical movements in tertiary planes. For each individual subject, retest gave the same findings.

In Figure 5, the right lateral rectus shows greater activity in the up and right position as compared to the down and right position, whereas in Figure 6, the right lateral rectus is more active in down and right gaze (Fig. 6*A*) as compared with up and right gaze (Fig. 6*B*).

The medial rectus, too, shows this inconsistency. In Figure 7, the left medial rectus shows greater activity in down and right gaze as compared with up and right gaze, whereas in Figure 8, the left medial rectus shows greater activity in up and right gaze as compared with the down and right position. The inhibited left lateral rectus in both instances shows no change.

D. Vertical Movements in Left Field of Gaze

In this field of gaze, the medial and lateral rectus muscles continue to show no consistent pattern of activity in vertical movements.

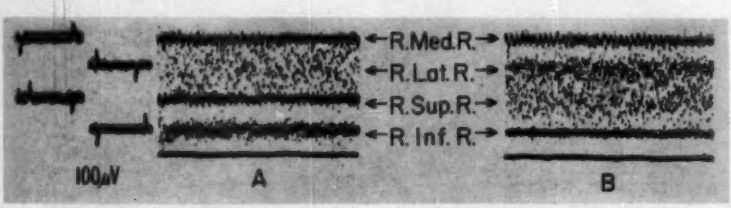
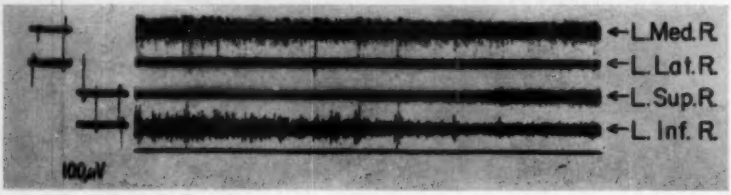


Fig. 6.—*A*, the right eye in down and right gaze; *B*, the same eye, a moment later, in up and right gaze. Note increased right lateral rectus activity in the lower field of gaze.

In Figure 9, the right medial rectus is more active in down and left gaze as compared with up and left gaze, whereas in Figure 10 the reverse is found. In Figure 9, the left lateral rectus is more active in down and left gaze as compared with up and left gaze, whereas in Figure 11 the reverse is noted.

In vertical movements both in right and left fields of gaze it was sometimes noted that the active horizontal muscles showed

Fig. 7.—The left eye is moving from down and right to up and right gaze. Note increased left medial rectus activity in lower field and no change in activity of inhibited left lateral rectus.



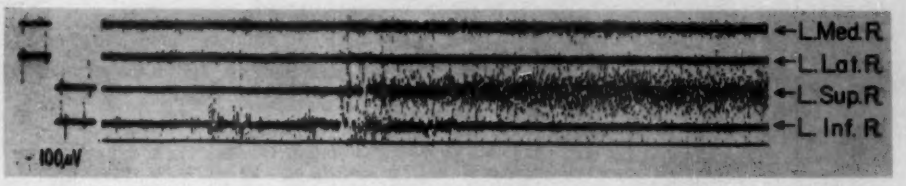


Fig. 8.—The left eye is moving from down and right to up and right gaze in another patient. Now left medial rectus activity is greater in upper field. Again there is no change in activity of the inhibited left lateral rectus.

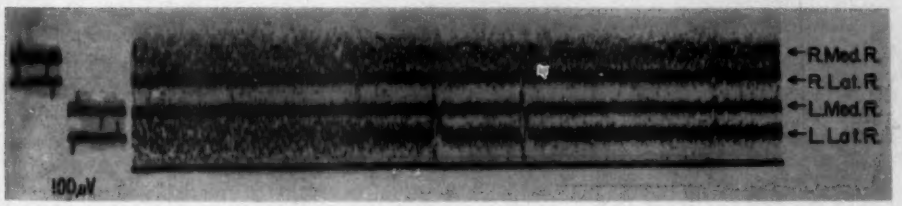


Fig. 9.—The right eye is moving from down and left gaze to up and left gaze. Note that the right medial rectus and left lateral rectus are more active in the lower field of gaze.

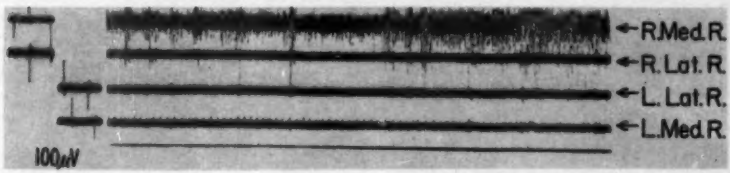


Fig. 10.—In another patient, the right eye is moving from down and left to up and left gaze. Now the right medial rectus is more active in the upper field of gaze, whereas the left lateral rectus shows no significant change.

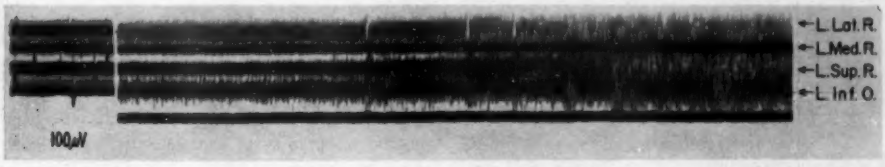
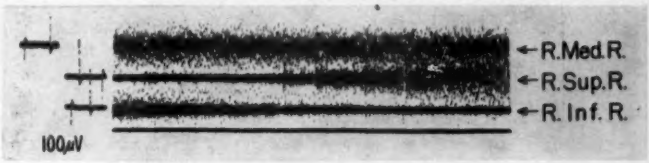


Fig. 11.—Left eye moving from down and left to up and left gaze. Now left lateral rectus is more active in upper field (compare with Figure 9).

Fig. 12.—The right eye is moving from down and left to up and left gaze. There is no significant change in right medial rectus activity.



no significant change in electrical activity. For example, in Figure 12, the right medial rectus muscle shows no significant change in activity as the right eye moves from down and left to up and left gaze.

Comment

The consistent findings of greater activity of the vertical recti in abduction and of the inferior oblique in adduction during following movements between tertiary positions is in agreement with similar findings by Breinin.[3] On the other hand, we have found no consistent variation in activity from subject to subject of the horizontal recti in vertical following movements between tertiary positions of the eye. Momosse[4] found no significant change in activity of vertical recti in horizontal movements 23 degrees above and below the horizontal and in the horizontal recti in vertical movements 23 degrees to the right and left of the vertical. Had he chosen his horizontal and vertical tertiary planes farther from the primary position, he probably would have obtained changes similar to ours and Breinin's.

We cannot, at this time, offer a satisfactory explanation relative to the constant increase in activity of the vertical recti in abduction and the inferior oblique in adduction in tertiary plane following movements. Whether this is due to anatomical, torsional, or other requirements is not clear at the moment. It is to be remembered that there is no significant systematic change in electrical activity of any of the extraocular muscles acting as auxiliary muscles during following movements in horizontal and vertical planes through the primary position.[1]

Neither can we explain the different alterations of various subjects in horizontal recti activity during vertical following movements between tertiary positions. The mechanism of peripheral proprioceptive feedback[5-7] offers an attractive field for speculation and future research.

Breinin[8] attempts to explain the A or V syndrome[9] on the basis of changes in activity of the horizontal recti during vertical movements. In a few of his cases of this syndrome, the horizontal recti exhibited no particular change in vertical gaze. Here, by exclusion, he ascribes the incomitance to the vertical muscles. Because of the normal variation in activity of the horizontal recti in tertiary plane movements, it appears misleading to draw conclusions regarding causation of the A or V syndrome without at least adequate sampling. Furthermore, the mere presence of increased activity of the muscles may only reflect the new position of the eye rather than tell us why the eye moved to this new position. For example, if the eye of an exophore is covered, that eye will deviate outward under cover and the electromyogram will show increased activity of the lateral rectus of that eye. This does not mean that an abnormally overactive lateral rectus muscle caused the exophoria. It simply means that the eyes are moved by eye muscles and that, in this case, the deviated eye was pulled outward by its lateral rectus muscle.

Conclusions

In horizontal following movements between tertiary positions the vertical recti are consistently more active in abduction than adduction, whereas the reverse is true for the inferior oblique. The horizontal recti manifest no consistent pattern of electrical alteration from subject to subject in vertical tertiary plane following movements. Possible changes in coactivity could not be successfully detected during following movements of the eye between tertiary positions of gaze because of the masking effect of reciprocal inhibition of one member of the normal agonist-antagonist pair.

Valuable assistance in these studies was contributed by Mr. William Houweling, Mr. John Williams, and Mr. Bob Markowitch, electronics engineers; Mr. Wilmer Renner, photographer, and Niles Roth, B.A., M.O.

Stanford University Hospitals, Clay & Webster Sts. (15).

REFERENCES

1. Tamler, E.; Marg, E., and Jampolsky, A.: An Electromyographic Study of Coactivity of Human Extraocular Muscles in Following Movements, A. M. A. Arch. Ophth. 61:270, 1959.

2. Marg, E.; Jampolsky, A., and Tamler, E.: Elements of Human Extraocular Electromyography, A. M. A. Arch. Ophth. 61:258, 1959.

3. Breinin, G. M.: Quantitation of Extraocular Muscle Innervation, A. M. A. Arch. Ophth. 57:644, 1957.

4. Momosse, H.: Studies on the Action of the Extraocular Muscles in Monocular Movements by Means of Quantification of Integrated EMG, Acta ophth. japon. 61:1570, 1957.

5. Granit, R.: Receptors and Sensory Perception, New Haven, Conn., Yale University Press, 1955.

6. Ludvigh, E.: Control of Ocular Movements and Visual Interpretation of Environment, A. M. A. Arch. Ophth. 48:442, 1952.

7. Cooper, S., and Daniel, P. M.: Responses from the Stretch Receptors of the Goats Extrinsic Eye Muscles with an Intact Motor Innervation, Quart. J. Exper. Physiol. 42:222, 1957.

8. Breinin, G. M.: New Aspects of Ophthalmoneurologic Diagnosis, A. M. A. Arch. Ophth. 58:375, 1957.

9. Urist, M. J.: Horizontal Squint with Secondary Vertical Deviations, A. M. A. Arch. Ophth. 46:245, 1951.

Ocular Pressure Patterns in the Valsalva Maneuver

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It has been recognized for many years that the intraocular pressure follows acute alterations in blood pressure.[1,2] Thus, acute elevation of arterial pressure is associated with a rapid and unsustained rise of ocular pressure, while a fall in arterial pressure, such as follows ligation of the inferior vena cava, results in a transient fall in ocular pressure. Likewise, alterations in the venous pressure in the head and eye are associated with similar changes in the ocular pressure, as illustrated by the elevation of intraocular pressure when the jugular vein is compressed or the vortex or anterior ciliary veins are ligated.[3,4] These alterations are most readily interpreted as resulting from changes in the intraocular blood volume. One would not expect changes in aqueous inflow or outflow or in rigidity of the ocular coats to result in such immediate changes.

The Valsalva maneuver, a procedure in which the intrathoracic pressure is raised by an expiratory effort, produces a variety of hemodynamic responses (Fig. 1). Salient among these in patients with normal cardiac reserve are an increase in peripheral venous pressure, a fall in systolic, diastolic, and pulse arterial pressures, and a subsequent overshoot in the latter values.[5] Since the changes in arterial and venous pressures take place in opposite directions, it was considered worth while to assess the effect of this procedure on the intraocular pressure. In carrying out the Valsalva maneuver on patients during the course of clinical tonography, several intraocular pressure patterns were observed.

Submitted for publication May 16, 1959.

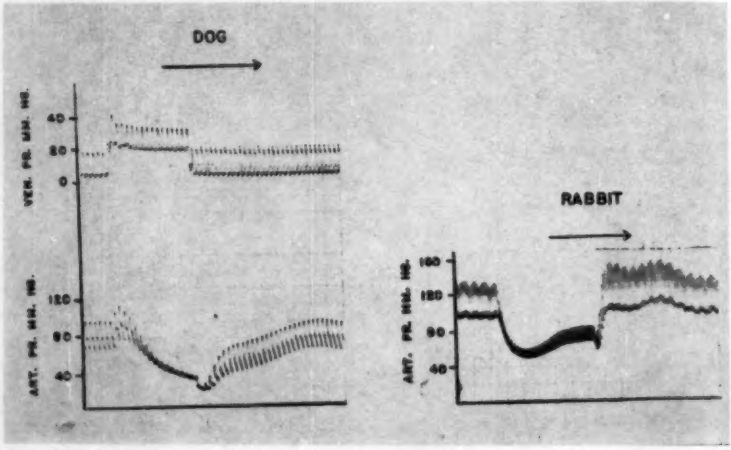
Department of Ophthalmology, Queen's University.

This work was supported by Grant No. M. A. 519 of the National Research Council of Canada.

Methods

Tonography was performed with a Mueller electronic tonometer linked to a Leeds and Northrup Type G Speedomax Re-

Fig. 1.—Effect of the Valsalva maneuver on arterial and venous pressures.



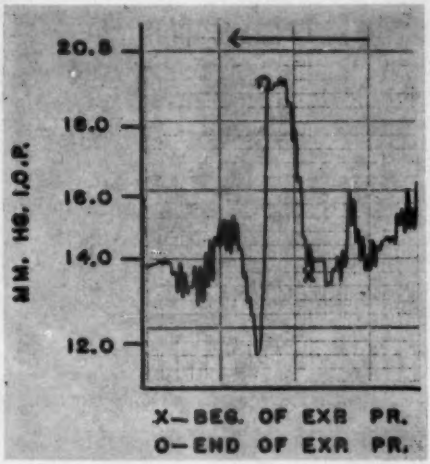


Fig. 2.—Examples of positive response in Valsalva maneuver.

corder. The Valsalva maneuver was carried out by having the supine subject take a full inspiration and exhale forcibly for 10 seconds at a pressure of 30 or 40 mm. of mercury into a closed mercury manometer.

Results

Two principal ocular pressure patterns were observed. For simplicity, one will be described as a positive pattern, in which the primary alteration is an increase in intraocular pressure, and the other as a negative pattern, where the most striking alteration is a fall in intraocular pressure.

A number of forms of the positive response were noted:

(*a*) A sharp increase in intraocular pressures sustained for the duration of the blow and followed by a transient fall below the base line and by a secondary overshoot lasting 5 to 10 seconds (Fig. 2).

(*b*) A sharp rise in intraocular pressure persisting throughout the expiration and followed by a fall to the base line and a secondary rise above it (Fig. 3).

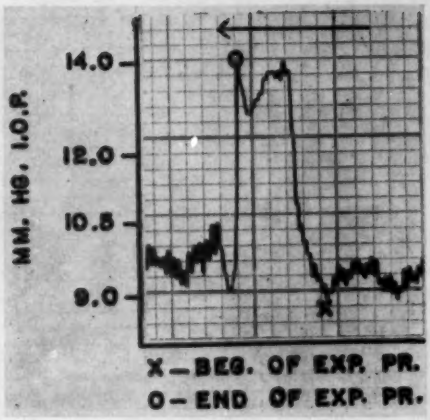


Figure 3

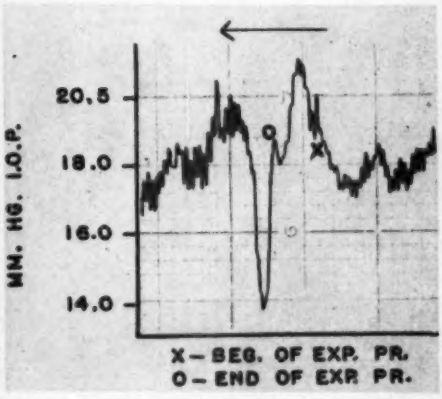


Figure 4

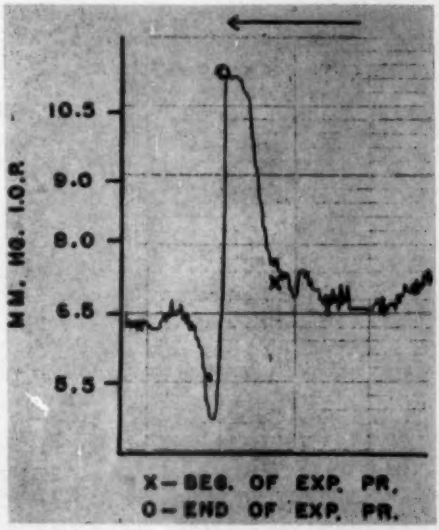


Figure 5

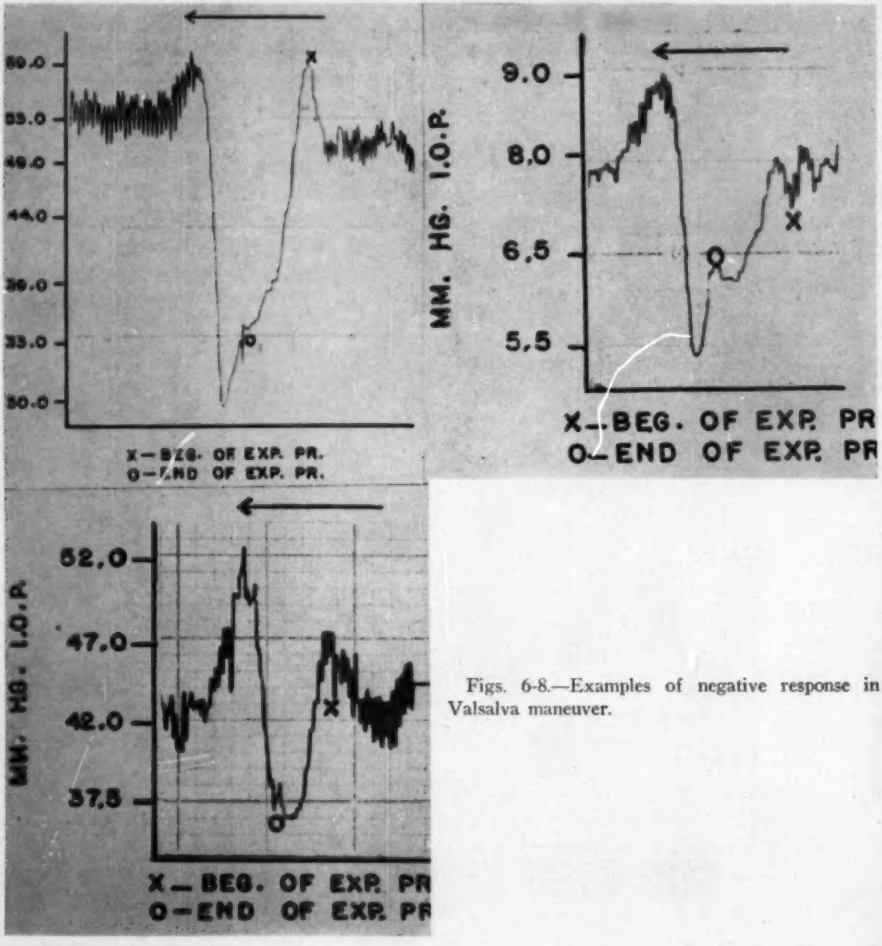
(*c*) An initial increase in intraocular pressure followed by a decline during the maintenance of the expiratory effort. After cessation of the blow a rapid fall below the base line and a secondary overshoot developed (Fig. 4).

(*d*) A rapid and sustained increase of intraocular pressure during the expiration succeeded by a fall below the base line upon its termination and a return to the base line without an overshoot (Fig. 5).

In the negative response there was a precipitous fall in intraocular pressure, either immediately upon initiation of the expiratory force or after a brief and minor rise of intraocular pressure. Upon discontinuing the blow there was usually an additional decline of ocular pressure followed by a recovery of the base line with or without an overshoot above base (Figs. 6-8).

The pattern followed was usually identical in the two eyes of a given patient, and successive determinations on the same eye usually yielded similar results.

The force of the expiratory effort was found to have considerable influence on the magnitude of the ocular pressure response, as illustrated in Figure 9, which depicts an almost linear increase of the intraocular



Figs. 6-8.—Examples of negative response in Valsalva maneuver.

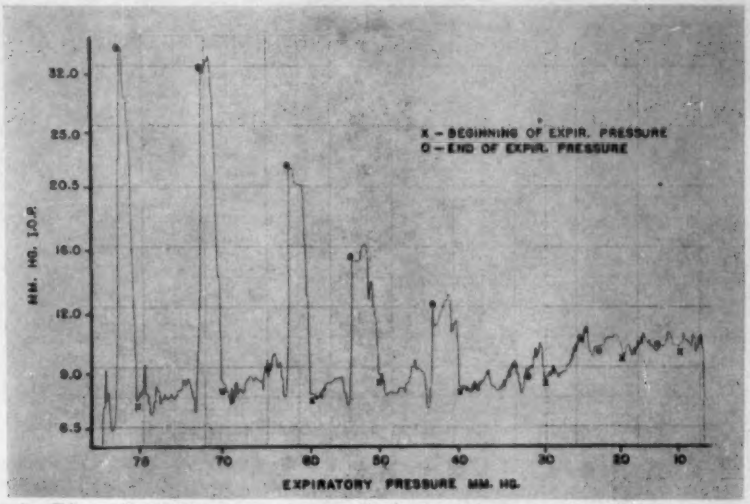
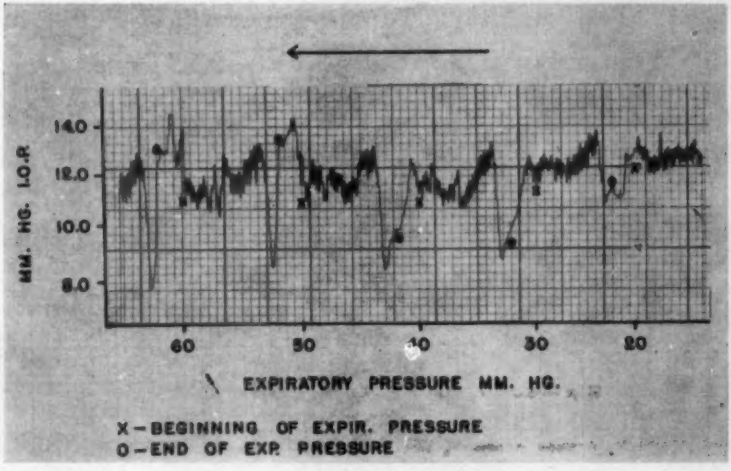


Fig. 9.—Effect of expiratory pressure on amplitude of positive response in Valsalva maneuver.

pressure rise with increasing force of the expiration. Negative responses were found to alter to a positive deflection at expiratory pressures of 50 mm. of mercury or greater (Fig. 10). Expiratory pressures of 30 and 40 mm. of mercury were elicited from all the subjects of this report, as occasionally the lower level failed to yield a response which could be interpreted. In the analysis which follows, only those subjects in which clear-cut results were obtained and in which the type of ocular pressure change was similar at the two expiratory pressures were admitted. The magnitude of the pressure rises or falls in the positive and negative patterns bore no consistent relationship to the initial intraocular pressure, as illustrated in Figures 11 and 12, which indicate responses of similar magnitude at widely varying ocular pressures.

Tables 1 and 2 summarize our experience with 251 patients. Of these, 198 are labeled as normal. These are patients who, while

Fig. 10.—Influence of expiratory pressure on the negative response in the Valsalva maneuver.



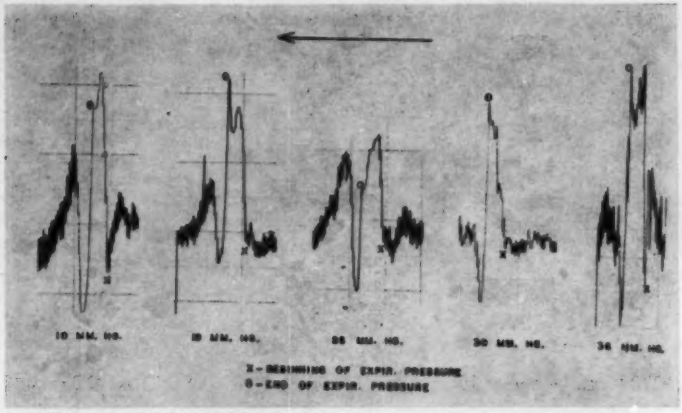


Fig. 11.—Similar positive responses at various intraocular pressures.

having a variety of ocular disturbances, such as refractive errors, cataract, vascular retinopathies, and macular degeneration, had normal intraocular pressure and aqueous outflow facility.

A total of 53 patients with a variety of primary and secondary glaucomas were studied. Their glaucoma was considered to be out of control [6] when the ratio of P_o/C was found to be over 100 and controlled when this ratio was under 100. This ratio was adopted for this study, as a number of the subjects revealed conflicting variations of each of the moieties of this ratio

Fig. 12.—Similar negative responses at various intraocular pressures.

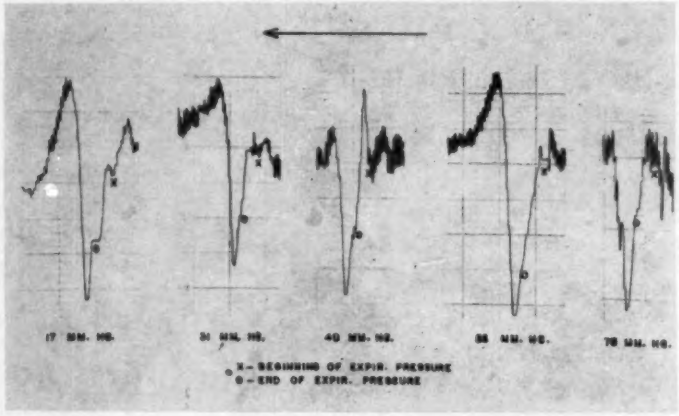


TABLE 1.—*Summary of Valsalva Studies in Two Hundred Fifty-One Patients*

Category	No. Studied	Positive No.	Positive %	Negative No.	Negative %
Normal (nonglaucoma)	198	183	92.4	15	7.6
Uncontrolled glaucoma, all types ($P_o/C>100$)	41	11	28.8	30	71.2
Controlled glaucoma ($P_o/C<100$)	38	24	62.2	14	36.8

which would have made a classification of their status on the basis of P_o or C alone impossible.

Of the 198 patients classified as nonglaucomatous, 183 (92.4%) had a positive ocular pressure deflection in the Valsalva maneuver, while 15 (7.6%) yielded a negative response. Of the 53 glaucoma subjects, 31 were investigated both before and after

TABLE 2.—*Summary of Valsalva Studies in Fifty-Three Glaucoma Patients*

Type of Glaucoma	No. Studied	Uncontrolled $P_o/C>100$				Controlled $P_o/C<100$			
		Positive		Negative		Positive		Negative	
		No.	%	No.	%	No.	%	No.	%
Chronic simple	25	5/21	23.8	16/21	76.2	12/20	60.0	8/20	40.0
Angle-closure	10	1/5	20.0	4/5	80.0	7/9	77.8	2/9	22.2
Secondary glaucoma *	18	5/15	33.3	10/15	66.7	5/9	55.6	4/9	44.4
Total	53	11/41	28.8	30/41	71.2	24/38	63.2	14/38	36.8

* Including lens dislocation (3), capsule exfoliation (3), hypermature cataract (1), aphakic (4), central vein occlusion (3), post-traumatic (2), melanoma of choroid (1), and iritis (1).

control by surgical or medical measures. Additional subjects were studied only when in or out of control and were included in the total of 41 with uncontrolled and 38 patients with controlled glaucoma. The results obtained were similar in patients with chronic simple, angle-closure, and secondary glaucomas and are summarized in Table 2. Of the 41 patients with uncontrolled glaucoma, 11 (28.8%) had a positive response, while 30 (71.2%) had a negative pressure deflection. In the group of 38 patients with controlled glaucoma, 24 (63.2%) had a positive reaction, while 14 (36.8%) had a negative response. There was no correlation between the initial pressure level or extent of pressure decline with treatment and the direction of pressure change in the Valsalva maneuver. Nor was the magnitude of the pressure change influenced by the intraocular pressure level (Fig. 12).

Statistical analysis of these data reveals that the difference between the normal and uncontrolled glaucoma group is highly significant ($P<0.01$). Comparison of the group of the glaucoma patients before and after control likewise reveals a difference which is statistically valid ($0.01<P<0.02$).

Comment

The positive response pattern observed in the Valsalva maneuver is readily explained on the basis of the hemodynamic alterations which are known to occur in this experiment. The elevated venous pressure may be communicated through the jugular, orbital, and vortex veins to the choroid, bringing about a vascular engorgement and increase in the volume of this tissue. This comes about despite the associated lowering of arterial pressure and gives rise to a rapid increase of intraocular pressure. In some subjects, however, perhaps because of anatomical differences in the distribution of arteries and veins, the increased choroidal blood volume cannot be sustained in the presence of a falling arterial pressure head and the initial increase gives way to a fall. The decrease in intraocular pressure which follows cessation of expiratory effort may result from evacuation of choroidal blood when the venous pressure falls and local reflex vasoconstriction accompanying the fall in systemic blood pressure, while the final overshoot when present may be the result of the final elevation of arterial pressure as well as reflex vasodilatation in the choroid.

It is somewhat more difficult to account for the negative response seen in a number of normal subjects and in a majority of eyes with uncontrolled glaucoma. Here one must assume that the falling arterial pressure head overshadows the elevation of venous pressure and that a decrease in intraocular blood volume and intraocular pressure is the net result of these hemodynamic events.

In speculating about the relationship of glaucoma to the development of the negative response, one may wonder whether the elevated intraocular pressure acts as a tampon preventing the overfilling of the

choroidal blood vessels which would be expected when the venous pressure increases. The lowered arterial pressure would, under these circumstances, account for a diminution of choroidal volume and a lowered intraocular pressure. This would not explain the variations in the magnitude of the ocular pressure fall which was seen to be unrelated to the initial level of intraocular pressure.

Such an hypothesis also does not account for the 28.8% of uncontrolled glaucoma patients in which a positive response was elicited, a group wherein the intraocular pressure did not vary significantly from the majority group in which a negative response was observed. Nor does it account for the 7.6% of normal subjects in which a negative pattern occurred. One may wonder about the role of anatomical differences in the arterial and venous blood supply to the eye or differences in the rigidity of choroidal blood vessels in determining this behavior.

The hypothesis of a tampon effect of the intraocular pressure would explain the reversal of response observed when glaucoma was brought under control. One wonders, however, why the lowering of ocular pressure was not universally effective in reversing this response, as the degree of tension-lowering was no different in the group which experienced the reversal from that in which a negative response persisted.

Somewhat similar observations were made by Wessely,[1,2] when he detected in rabbits that the percentage rise in intraocular pressure for a given increase in arterial pressure decreases with rising intraocular pressure and that a given lowering of arterial pressure produces a greater fall in intraocular pressure, the greater its initial height. Davson,[7] in commenting on these findings, discounts the possibility of an influence of scleral distensibility, as one would anticipate larger effects on the intraocular pressure when this is high than when it is low.

Summary

A group of 251 patients, including 198 normal subjects and 53 with glaucoma, were investigated by the Valsalva maneuver performed during tonography.

Of the 198 normal subjects, 183 exhibited an increase and 15 a decrease of intraocular pressure.

Of the 41 patients with uncontrolled glaucoma, 11 presented an increase while 30 presented a decrease of intraocular pressure.

A positive response was elicited in 24 and a negative response in 14 of 38 patients with controlled glaucoma.

These results are statistically significant.

An interpretation of these results is offered in the text.

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REFERENCES

1. Wessely, K.: Experimentelle Untersuchungen über den Augendruck, sowie über qualitative und quantitative Beeinflussung des intraokularen flüssigkeitswechsels, Arch. Augenh. 60:1-48 and 97-160, 1908.

2. Wessely, K.: Weitere Beiträge zur Lehre vom Augendruck, Arch. Augenh. 78:247-278, 1915.

3. Adamiuk, E.: De l'Etiologie du glaucome, Ann. ocul. 58:1-13, 1867.

4. Bartels, M.: Über Blutgefässe des Auges bei Glaukom und über experimentelles Glaukom durch Versperrung von vorderen Blutbahnen, Ztschr. Augenh. 14:258-289, 1905.

5. Judson, W. E.; Hatcher, J. D., and Wilkins, R. W.: Blood Pressure Responses to the Valsalva Maneuver in Cardiac Patients With and Without Congestive Heart Failure, Circulation 11:889-899, 1955.

6. Becker, B., and Christensen, R. E.: Water-Drinking and Tonography in the Diagnosis of Glaucoma, A. M. A. Arch. Ophth. 56:321-326, 1956.

7. Davson, H.: Physiology of the Ocular and Cerebrospinal Fluids, London, J. A. Churchill, Ltd., 1956, p. 319.

Studies on Intraocular Effects of the Orbital Parasympathetic Pathway

III. Effect on Steady-State Dynamics

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The effects of electrical stimulation of the orbital parasympathetic pathway in the cat on the chamber angle and meshwork and on the intraocular pressure,[1,2] as reported previously, pointed towards a possible associated increase in the facility of outflow of aqueous. This possibility was specifically investigated in 105 experiments in the anesthetized cat, as well as in the enucleated eye. The results, which will be the subject of this communication, revealed that during parasympathetic stimulation there was a marked increase in the facility of outflow which was due entirely to the activity of the ciliary muscle rather than to the associated constriction of the pupil.

Techniques

This presentation will be limited to the details of the constant-pressure perfusion and the constant-rate perfusion techniques, because they provide a measurement of the outflow facility which is independent of the elasticity constant of the eyeball and of elasticity changes that might accompany parasympathetic stimulation.[3]

Constant-Pressure Perfusion Technique. In this technique[5-7] the outflow facility during a certain steady state is measured by observing the rate of inflow of fluid from an external source cannulated to the eye at a certain experimental pressure.

Submitted for publication May 18, 1959.

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This investigation was supported in part by Research Grant B-1689 from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

At steady state, the rate of fluid inflow into the eye from intraocular sources (I_s in cubic millimeters per minute) is equal to the rate of fluid outflow into extraocular vessels. This outflow is accomplished with a limited facility (C in cubic millimeters per millimeter of mercury per minute) determined by the intervening outflow passages. This limitation produces a pressure gradient (P_g in millimeters of mercury) between the intraocular space and the extraocular vessels which at steady state can accomplish this transfer of fluid at a rate equal to the rate of inflow.

If at steady state the pressure in the extraocular vessels is P_v in millimeters of mercury and that in the intraocular space P_o in millimeters of mercury, the relationship between the various parameters may be expressed as follows:

$$I_s = P_g \times C = (P_o - P_v) \times C$$

When an eye maintaining a certain Steady State 1

$$(P_{o_1} - P_{v_1}) \times C_1 = I_{s_1} \qquad (1)$$

is cannulated to an external source containing fluid similar to intraocular fluid at an experimental pressure P_e in millimeters of mercury ($P_e > P_o$), fluid will flow from the external source to raise P_o to P_e and to establish a new Steady State 2

$$(P_e - P_{v_2}) \times C_2 = I_{s_2} + I_{s_2} \qquad (2)$$

where I_{s_2} is the rate of flow in cubic millimeters per minute from the external source during the experimental Steady State 2.

Similarly, if Steady State 1 is changed by the action of a certain agent to Steady State 3

$$(P_{o_3} - P_{v_3}) \times C_3 = I_{s_3} \qquad (3)$$

and Steady State is then changed to Steady State 4 by perfusing at P_e; then for Steady State 4 we can write

$$(P_e - P_{v_4}) \times C_4 = I_{e_4} + I_{s_4} \qquad (4)$$

Evidently, in order to obtain a measurement of C at any steady state a simultaneous measurement of each of the remaining variables is essential. In this study no such measurements were available for I_e or for P_v. Instead, in order to obtain from Equations 2 and 4 a numerical value related to the outflow facility at Steady States 1 and 3, the following assumptions were made, 1. that the experimental procedure of perfusing isotonic saline into the anterior chamber does not alter I_{v_1} and C_1 or I_{e_3} and C_3; 2. that for values of P_e used, C_1, I_{e_1}, C_3, and I_{e_3} remained unchanged; 3. that the change in P_v, when P_{e_1} or P_{e_3} is raised to P_e, may be considered the same and the effect of its elimination from Equations 2 and 4 may be considered similar for identical values of P_e and for relatively minor differences between P_{e_1} and P_{e_3}.

Then by substitution and elimination of P_{v_1} and P_{v_3} we can write for Steady State 2

$$(P_e - P_{e_1}) \times C'_1 = I_{s_2}$$

and for Steady State 4

$$(P_e - P_{e_3}) \times C'_3 = I_{s_4}$$

where C'_1 and C'_3 are numerical values influenced by C_1 and C_3 (the facility of outflow at Steady States 1 and 3), as well as by the deviation from the assumptions of the unmeasured parameters I_e and P_v. Thus, a difference between C'_1 and C'_3, greater than that which can be explained by reasonable deviations of I_e or of P_v, will reflect *qualitatively* the difference between C_1 and C_3. This difference will be reported as a percentage.

In the *enucleated eye*, these assumptions are not required; a quantitative measurement of the outflow facility is obtained from accurately measured parameters. The formulation at any steady state becomes

$$P_e \times C = I_s.$$

Constant-Rate Perfusion Technique.—In this technique, Steady States 2 and 4 are produced by perfusing fluid into the eye at a certain constant rate, I_s, which produces a certain level of equilibrium pressure, P_e (Figs. 6 and 7). By accepting the assumptions already mentioned, the formulations developed for the first technique become applicable here.

While this technique did not improve the definitive content of C', it helped validate the results obtained by the first technique where an especially designed apparatus was utilized.

Apparatus

An apparatus was designed with which the desired experimental pressure levels can be quickly attained and accurately maintained and with which the volume and rate of fluid exchange in the external source is continuously and accurately recorded (Fig. 1).

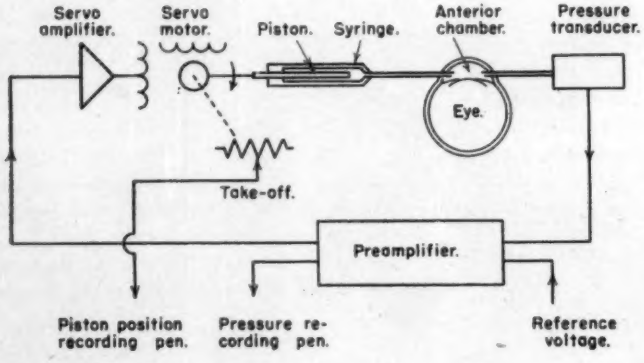


Fig. 1.—Block diagram of servo-perfuser.

It utilized a servo-mechanism in which the reversible motor of the perfusion pump was activated in the proper direction by the difference, or error, between a desired or reference electrical input and the actual value of electrical output. The proper direction is that which tends to eliminate the error (Fig. 1). The zero-suppression device of Model 150-1100 AS Sanborn Carrier Preamplifier provided the desired input accurately calibrated in millimeters of mercury and with which the actual output of a Model 267B Sanborn Pressure Transducer, monitoring the intraocular pressure, was to be continuously compared.

When the loop is closed by cannulating the perfusion pump and the transducer to the eye, an automatic regulating mechanism results with which step changes in intraocular pressure can be quickly produced and accurately maintained. The simultaneous record of fluid exchange in the perfusion pump provides a measurement of the volume required to produce step changes in pressure and of the rate, I_s, required to maintain constant a certain pressure level, P_e.

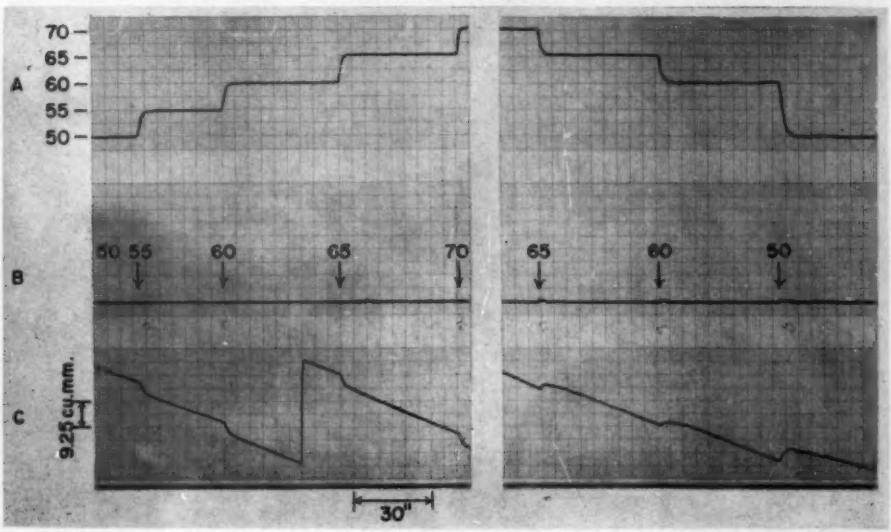
When $P_e=P_o$, $I_s=0$; when $P_e=P_v$, $I_s=I_e$.

The volume record was obtained by allowing the motor shaft which moves the piston of the perfusion pump to move the wiper of a potentiometer whose output was continuously monitored by the appropriate channel.

The performance of this system between 10 and 100 mm. Hg was tested by connecting it to a manometer. The pressure in millimeters of mercury generated in the manometer was compared with that set at the dial. The difference occasionally exceeded $\pm 1\%$ but was less than $\pm 2\%$.

It was further tested in the eye, where a leak exists at the outflow channels, by cannulating another transducer independently to monitor the intraocular pressure.

Fig. 2.—Performance of the servo-perfusor in the enucleated eye. *A*, the intraocular pressure recorded by a pressure-transducer cannulated independently into the anterior chamber; *B*, records the difference between the pressure set at the "reference" dial (recorded in millimeters of mercury on the chart) and that recorded by the loop-transducer cannulated into the anterior chamber. Equality of the two pressures is indicated by maintaining the stylus on the base line. *C*, records position of the perfusion piston. Movement forward is reflected as a downward displacement of the stylus. Note the difference in the rate of change when a step-rise in pressure is introduced at the reference dial until a "steady state" is arrived at. Simultaneous comparison of these records indicates the adequacy of the performance of this system.



The difference between the pressure recorded by the independent transducer and that at the dial setting did not exceed ±1% and was maintained without a detectable change by the activity of the servoperfusor (Fig. 2). Step changes in pressure were executed in 1-7 seconds.

The accuracy of the volume record was tested by means of a pipet calibrated in cubic millimeters. The difference between the volume change estimated from the record and that actually read from the pipet did not exceed 1.0 cu. mm. for all piston positions and for volumes up to 40 cu. mm.

The error with which the slope of a certain tracing could be read after the initial 3-10 seconds did not exceed ±3% in the enucleated eye and ±10% in the living animal.

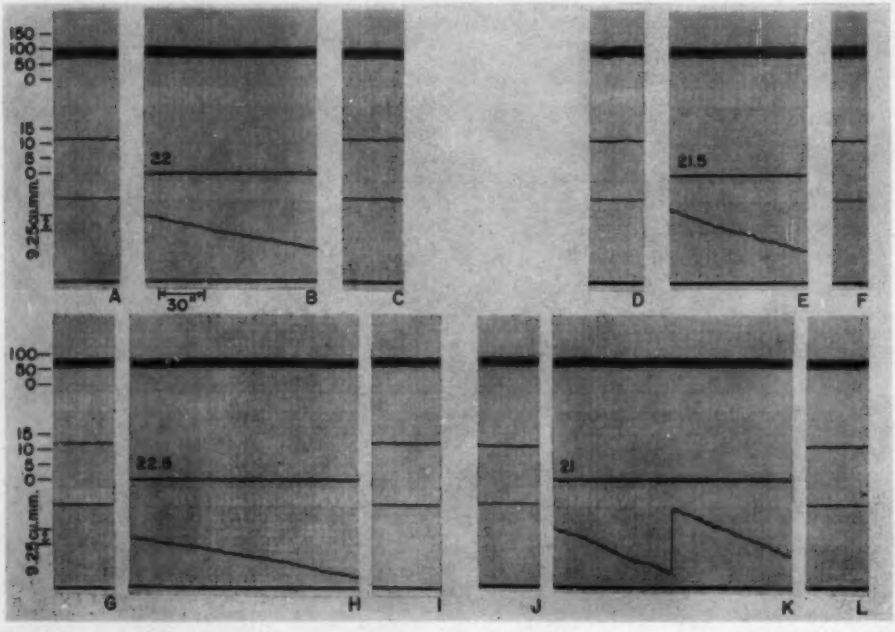
This apparatus could be quickly transformed into a constant-rate perfusion pump by shifting the motor control from the servo-input to a constant input which could be varied over a continuum, thus providing a wide range of constant-perfusion rates.

In addition, the Multispeed Perfusion Pump, of Harvard Manufacturers, which supplies various rates of perfusion, was used for the constant-rate perfusion technique.

Experimental Procedure

Under intrapleural pentobarbital (Nembutal) anesthesia the orbital parasym-

Fig. 3.—Facility determinations in the anesthetized cat: *A*, *B*, *C* and *G*, *H*, *I* during the unstimulated state followed by *D*, *E*, *F* and *J*, *K*, *L* during maintained stimulation. *A* and *G*, record the steady state P_o in the unstimulated state, before perfusion. *B* and *H*, record inflow from the servo-perfusor during the unstimulated state when the experimental pressure, P_e, is set at a level 10 mm. Hg higher than the P_o. *C* and *I*, record the steady state P_o during the unstimulated state after the servo-perfusor had been arrested and the eye allowed to recover from the perfusion procedure. Note that the steady-state pressures in the unstimulated state before and after the perfusion are identical. *D* and *J*, record steady-state pressure during maintained stimulation. *E* and *K*, record inflow from the servo-perfusor during maintained stimulation when P_e is set at a level 10 mm. Hg higher than P_o. *F* and *L*, record the steady-state pressure during maintained stimulation and after cessation of the perfusion: *C'* in *B*=1.23; *C'* in *H*=1.10; *C'* in *E*=1.85; *C'* in *K*=2.40. Stimulus intensity in *D*, *E*, and *F* was 3 volts; in *J*, *K*, and *L* it was 5 volts. Note the marked discrepancy between the magnitude of increase in *C'* values during stimulation and that of the reduction in P_o.

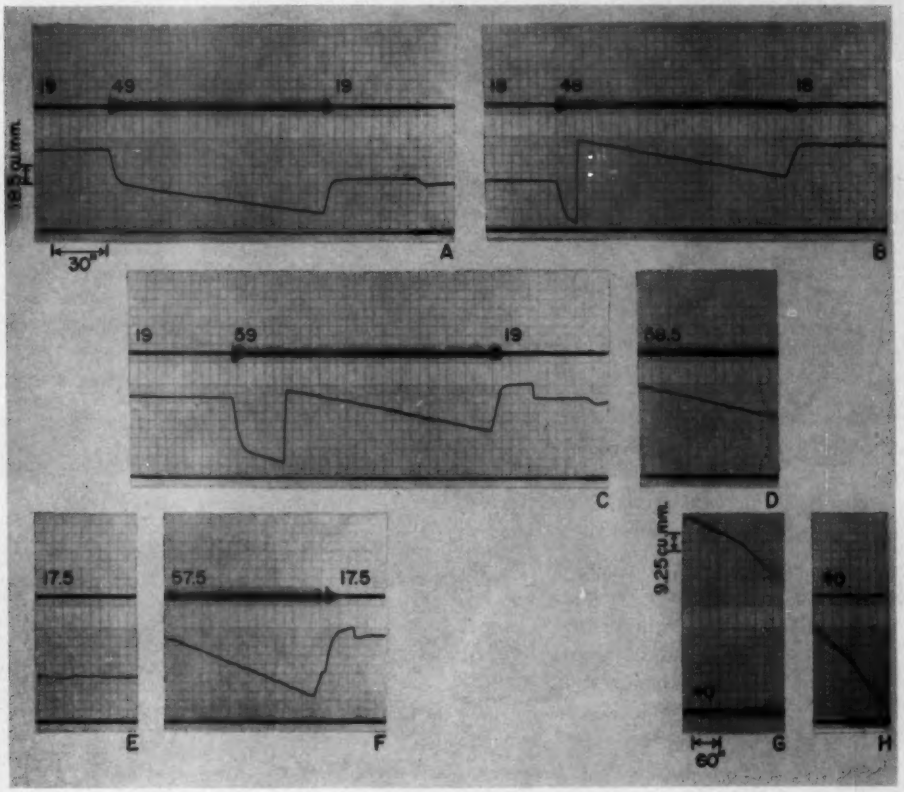


pathetic pathway was isolated, and the anterior chamber and the femoral artery were then connected to the appropriate transducers in the manner described previously.[1]

For a given experimental condition, each facility determination consisted of allowing the eye to establish a steady state for that condition, perfusing at a certain P_e or I_e during that condition, then arresting the external perfusion and allowing the eye to recover a final steady state under the same condition (Figs. 3-7). The difference in P_o of the steady state that preceded the determination at P_e and that which followed did not exceed ± 0.5 mm. Hg for the results and conditions reported in this publication.

Various levels of P_e and magnitudes of I_e were used. However, whenever facility

Fig. 4.—Facility determination in the anesthetized cat: *A* and *C* during the unstimulated state followed by *B*, *D*, *E*, and *F* during maintained stimulation. *G* and *H*, similar records in the enucleated eye. Servo-perfusor loop is closed thus: P_o is the pressure reading at the dial at which the rate of inflow from the servo-perfusor is equal to zero. *A*, *B*, *C*, *E*, and *F*, record the same triad of steady-state P_o, followed by perfusion at a certain experimental pressure, then cessation of perfusion and the development of a steady-state P_o. All these measurements were obtained during the same state of nonstimulation or of maintained stimulation. In *A* and *B* the experimental pressure, P_e, was 30 mm. Hg higher than the steady-state P_o. In *C*, *D*, and *F*, P_e was 40 mm. Hg higher than the steady-state P_o. Stimulus intensity in *B* and *D* was 5 volts; in *F* it was 7 volts. *C'* in *A*=0.51; *C'* in *B*=0.88; *C'* in *C*=0.55; *C'* in *D*=0.70; *C'* in *F*=1.06. *G*, records the inflow into the enucleated eye at an experimental pressure of 40 mm. Hg before and during stimulation: *C* before stimulation=0.36 cu. mm. per millimeter of mercury per minute; *C* during stimulation=0.65. *H*, another record similar to *G*: *C* before stimulation=0.58 cu. mm. per millimeter of mercury per minute; *C* during stimulation=0.91.



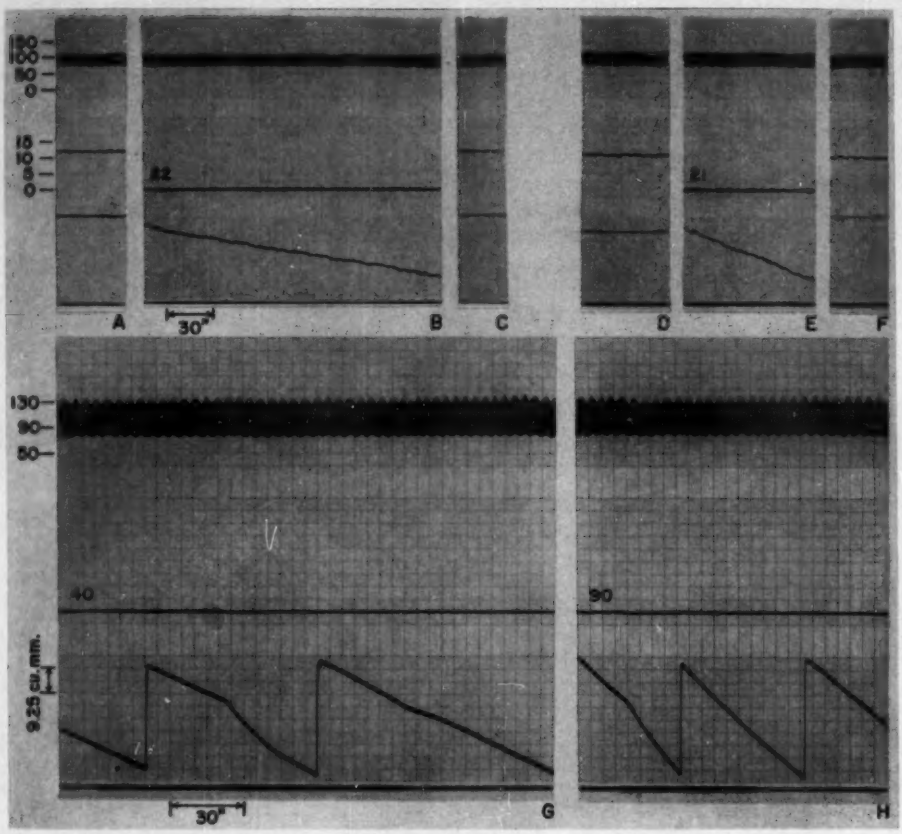


Fig. 5.—Facility determinations in the anesthetized cat: *A*, *B*, and *C* during the unstimulated state; *D*, *E*, and *F* during maintained stimulation. The triad is similar to that in Figure 3: *C'* in *B*=0.90; *C'* in *E*=2.22; stimulus intensity=5 volts. *G* and *H*, record the inflow required to maintain a certain P_e level constant without stimulation and during maintained stimulation. Note the increase in inflow rate during maintained stimulation.

estimates of two experimental conditions are compared, the comparison is made between results of determinations performed in succession during each of the two conditions with use of the same P_e or I_s.

In the anesthetized animal, when facility determinations were repeated with use of the same P_e or I_s, the difference between *C'* values obtained from any three successive determinations varied around ±10% and rarely reached ±15%. In the enucleated eye, this difference varied between ±5%.

When a larger number of repetitions was considered, an increase in *C'* values became manifest which in the anesthetized animal was accompanied by a reduction in P_o.

In the anesthetized cat when the same steady state was investigated with various levels of P_e or magnitudes of I_s, *C'* values obtained at high levels of P_e were significantly reduced compared with those obtained at lower levels. *C'* values obtained with a P_e of 50 mm. Hg were 20%-25% less than those obtained with a P_e of 20 mm. Hg. This observation was confirmed consistently in the enucleated eye.[4]

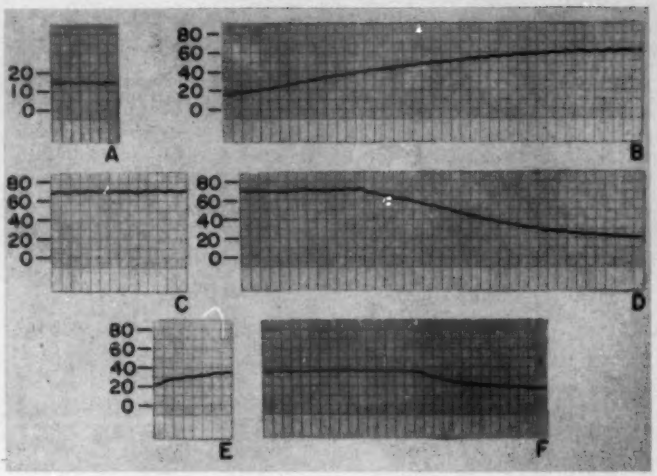


Fig. 6.—Constant-rate perfusion: *A*, *B*, *C*, and *D* in the unstimulated state; *E* and *F* during maintained stimulation. *A*, steady-state P_e in the unstimulated state =15 mm. Hg. *B*, records the intraocular pressure when fluid is perfused at a constant rate of 34 cu. mm. per minute into the anterior chamber: Note the approach to an equilibrium pressure and the maintenance of this pressure in *C* at a level equal to 65 mm. Hg and the reduction in pressure on cessation of the external perfusion with recovery of the same steady-state P_e as that before the perfusion. *C'* in the unstimulated state=0.68. *E* and *F*, record the change in intraocular pressure when the same rate is perfused during maintained stimulation. P_e during this state was 13 mm. Hg; the equilibrium pressure was 38 mm. Hg; on cessation of perfusion the eye recorded the same P_e; *C'* in the stimulated state=1.36.

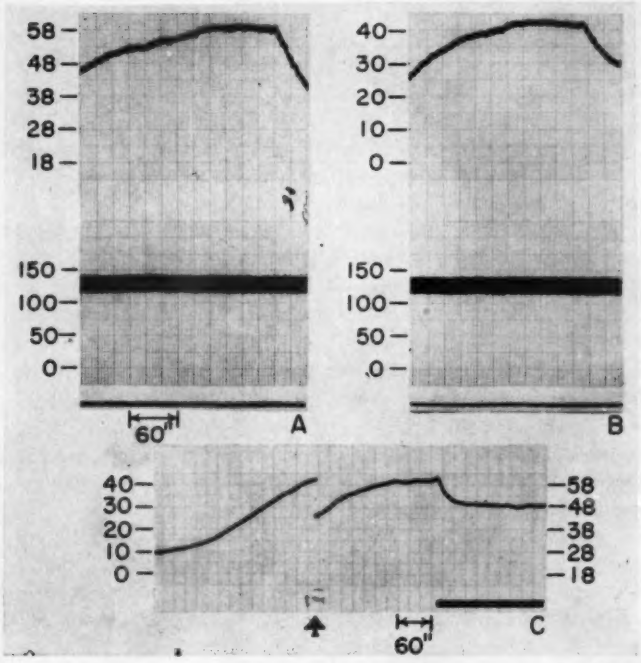


Fig. 7.—The equilibrium pressure for a constant rate perfusion of 34 cu. mm. per minute in the unstimulated state (*A*) and during maintained stimulation (*B*). In the unstimulated state, P_e=16 mm. Hg, P_e=60 mm. Hg, and *C'*=0.77. During maintained stimulation, P_e=14 mm. Hg, P_e=43 mm. Hg, and *C'*=1.17. *C*, records the intraocular pressure in the enucleated eye when the anterior chamber was perfused at a constant rate of 34 cu. mm. per minute. Lower arrow indicates the change of scale to that on the right-hand side. After the equilibrium pressure was reached, stimulation of the ciliary ganglion was started (solid line). Note the slight initial increase in pressure followed by a marked reduction and the maintenance of a lower level of equilibrium pressure during stimulation (P_e=49). *C* before stimulation=0.55 cu. mm. per millimeter of mercury per minute; *C* during stimulation=0.69.

The Effect on the Facility of Outflow of Eliminating the Parasympathetics

When the central connection of the isolated parasympathetic pathway was intact, the pupil appeared constricted to a vertical slit 1 mm. wide. When the connection of the preganglionic trunk to the third nerve was severed, the pupil dilated to a circular shape 8-10 mm. in diameter.[1]

Comparison of C' values obtained immediately before severing the central connection with those obtained immediately after revealed that this maneuver had produced a slight reduction in C' values. This reduction varied between 5%-20% and exceeded 15% in only 25% of the preparations.

The Effect of Stimulation of the Parasympathetic Pathway

In the anesthetized cat, stimulation of the ciliary ganglion with its *central connections intact* and the pupil constricted to a vertical slit produced a marked increase in C' values during stimulation (Figs. 3-7).

In general, the minimum effective stimulus[1] produced a simultaneous increase in C' values. However, on occasions, definite responses to stimulation[1] were manifest, including the reduction in intraocular pressure without an associated increase in C' values. If the intensity of the stimulus was then increased by 1-2 volts, C' values increased significantly (Figs. 3 and 4).

The magnitude of the increase in C' values during stimulation for a stimulus intensity of 3-5 volts ranged between 40%-100%.

This effect of stimulation was obtained in every preparation used. At no time did stimulation reduce C' values.

Of interest in this regard is that this increase in C' values was also obtained when, on occasion, the steady-state P_e during stimulation was equal to or higher than the prestimulus P_e level.[2]

When the P_e or I_s was kept constant, progressive increases in the stimulus intensity within the range of working voltage[1] produced progressively greater increases in C' values during stimulation until a maximum increment was reached.

When the intensity of stimulation was kept constant and C' values obtained with various levels of P_e, the increment in C' values during stimulation became smaller for higher levels of P_e.

However, when maximum response was sought for various levels of P_e, it was found that the maximum increment was greater for higher levels of P_e (Fig. 4).

The maximum increment in facility varied between 50% and 150%. It ranged between 50% and 100% for P_e levels lower than 50 mm. Hg and between 75% and 150% for those higher than 50 mm. Hg.

Stimulation of the ciliary ganglion *after its central connections had been severed* and the pupil widely dilated produced identical results, despite the fact that the pupil constricted only partially during stimulation.

When the dilated pupil was constricted to a vertical slit by perfusing the anterior chamber with 10μg. of 1/10,000 solution of pilocarpine, stimulation continued to produce the same effect on C' values. When the perfusion of pilocarpine was prolonged or a more concentrated solution was used, an increase in C' values was observed which varied between 30% and 50%. The increase in C' values during stimulation at this stage was either completely eliminated or reduced to a range of 25%-50%.

Atropine sulfate injected I. V. or into the anterior chamber in a dose that varied between 10μg.-40μg. per kilogram of body weight eliminated all responses to stimulation, including the effects on intraocular pressure and on C' values (Fig. 8).

In the *enucleated eye*, the results observed in the anesthetized cat were definitively confirmed (Figs. 4 and 7). An increase in outflow facility[7] comparable to or slightly greater in magnitude than that obtained in the anesthetized cat was observed during stimulation of the ciliary ganglion. The maximum increment in facility reached as high as 250%. In this preparation, how-

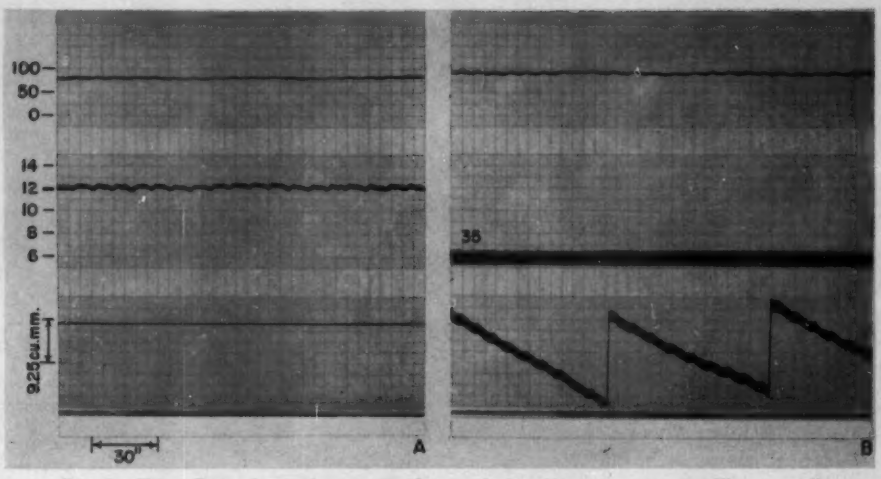


Fig. 8.—The effect of atropine on the intraocular pressure response to ciliary ganglion stimulation. Uppermost tracings record average arterial pressure. *A*, records the effect of stimulation of the ciliary ganglion on the steady-state P_e after an intravenous injection of 50μg. of atropine sulfate. Stimulus intensity of 13 volts produced a dilatation of the pupil and no effect whatsoever on the steady-state intraocular pressure. *B*, records the effect of a similar stimulation on the inflow required to maintain constant a P_e of 35 mm. Hg after the same dose of atropine sulfate. Note the complete elimination of the effect of stimulation on the inflow rate required to maintain a certain pressure level constant. The pupillary response was a dilatation.

ever, the intensity of stimulation was greater, in general, than that used in the anesthetized cat.[1] The reduction in pupil diameter from the dilated position during stimulation varied in the enucleated eye from 0-3 mm. However, the same increase in outflow facility occurred when the change in pupil diameter was minimal and only the manifestations of the ciliary muscle activity in the chamber angle and lens were evident.

The influence of variations in P_e level and in intensity of stimulation on the magnitude of increase in outflow facility during stimulation was similar to that reported for the anesthetized cat. Furthermore, eyes with initially low facility values tended to demonstrate a greater increase in facility of outflow during stimulation.

When the results obtained before stimulation were compared with those obtained after stimulation had ceased, no significant difference was found, indicating complete recovery.

The Effect of Trabeculotomy on the Response

Incision of the trabecular meshwork over a quadrant or more increased the facility of outflow to about 50%-150%. After trabeculotomy the increase in facility during parasympathetic stimulation was either completely eliminated or reduced to 15%-30%.

Furthermore, this procedure completely eliminated the effect of pilocarpine on outflow facility, despite the fact that the pupil diameter continued to change maximally.

The Effect of Sympathectomy

The effect of stimulation of the ciliary ganglion on intraocular pressure and outflow facility remained the same irrespective of whether or not a bilateral resection of the superior cervical ganglion had been performed.[1]

It is of interest that stimulation after atropine blockade in the nonsympathectomized group produced the sympathetic effect of active dilatation of the pupil without

any associated effect on intraocular pressure or on outflow facility (Fig. 8).

The Effect of Parasympathetic Stimulation on the Inflow Rate

The fact that facility increased even when the pressure during maintained stimulation was equal to or higher than the prestimulus pressure indicated that, under these circumstances, stimulation must have also increased either the rate of inflow of fluid into the eye or the pressure in the extraocular collector vessels or both.

By setting the P_e at 10 mm. Hg,* the servo-perfusor will draw fluid from the eye to maintain this pressure. The rate of this withdrawal is related to the inflow rate.

The rate of withdrawal was significantly increased during maintained stimulation, especially when stimulation produced a steady-state pressure equal to or greater than the prestimulus pressure (Fig. 9).

Comment

It is evident that the increase in C' values during parasympathetic stimulation in the anesthetized cat should be interpreted as reflecting an increase in outflow facility and not as reflecting merely a possible effect on the unmeasured parameters, I_e or P_v, or on the fluid exchange across the iris vessels.

The question of whether this effect was produced by the constriction of the pupil or by the contraction of the ciliary muscle is to be answered in favor of the latter. For, *in this preparation,* marked changes in pupil diameter from maximal constriction to wide dilatation and vice versa failed to change appreciably the outflow facility. Furthermore, stimulation affected outflow facility similarly, irrespective of the size of the pupil at the start and the magnitude of constriction during stimulation. Hence, the pupillary constriction during stimulation could not have been responsible for the associated increase in outflow facility.

The fact that trabeculotomy markedly reduced or eliminated the effect of stimulation on outflow facility indicates that stimulation reduced the resistance to outflow *at* the trabecular meshwork. The intimate connection of this meshwork to the fibers of the ciliary muscle, as well as the changes produced by parasympathetic stimulation in the chamber angle and meshwork, have been described in preceding publications.[1,4] It is justifiable to conclude that these changes constitute the mechanism that increased the outflow facility.

The effect of pilocarpine on the outflow facility and on the response to stimulation

* An assumed average for the pressure in the collector vessels for P greater than 15 mm. Hg.

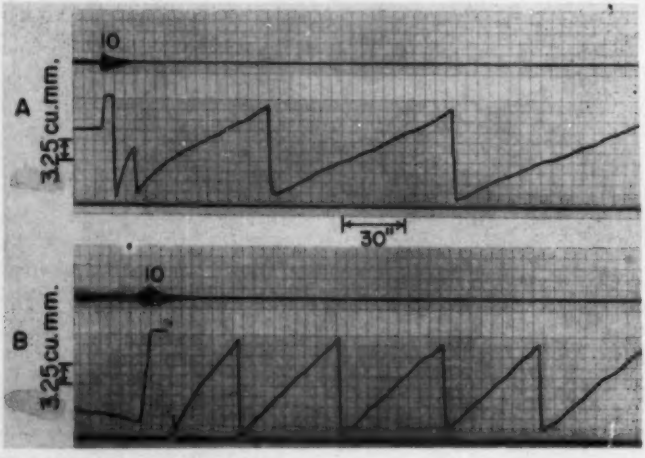


Fig. 9.—A record of the volume of fluid withdrawn from the eye before and during maintained stimulation in order to maintain constant a pressure level lower than the steady-state P_e. *A*, before stimulation: steady-state P_e=16 mm. Hg. The servo-perfusor maintains a pressure of 10 mm. Hg in the eye by withdrawing fluid at a rate of 9 cu. mm. per minute. *B*, during maintained stimulation: steady-state P_e=15 mm. Hg. The withdrawal rate required to maintain constant an intraocular pressure of 10 mm. Hg was equal to 19 cu. mm. per minute.

is to be explained by its action on the ciliary muscle rather than on the pupil and iris.

The fact that trabeculotomy eliminated the effect of pilocarpine on the facility of outflow, despite the associated maximal constriction of the pupil, leaves little doubt that *in this preparation* the effect on outflow facility was due to the reduction of the resistance to outflow at the trabecular meshwork. Furthermore, it shows that this effect on the meshwork was achieved by the action of pilocarpine on the ciliary muscle, not on the pupil.

The effect of pressure level on the outflow facility and on the increase in facility during stimulation indicates that both factors modify the resistance to outflow at the same site, namely, the trabecular meshwork.[1,4]

The increase in inflow rate during stimulation establishes two opposing and simultaneous effects of the parasympathetics on the dynamics of steady state. It provides a mechanism by means of which the eye can change the dynamics of steady state without changing the steady-state intraocular pressure level. This finding raises the question of whether the eye maintains a constant intraocular pressure by means of constant steady-state dynamics or whether it does so with changing dynamics which tends to maintain the intraocular pressure constant.

Another important question raised by this phenomenon is whether these antagonistic components of parasympathetic stimulation are inseparable or whether their association in these studies was due to the unselective character of the method of stimulation used and the site of the parasympathetics chosen and whether it is possible to separate these two components at a higher level in the central nervous system. Studies dealing with these questions will be reported in a future publication.

Lastly, the absence of any change in intraocular pressure or in facility of outflow, when stimulation after atropine blockade produced a sympathetic effect, is worthy of note. An extension of this finding to the sympathetics, in general, is not justified, since only a small fraction of the sympathetic fibers that innervate the intraocular structures go through the ciliary ganglion.

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REFERENCES

1. Armaly, M. F.: Studies on Intraocular Effects of the Orbital Parasympathetic Pathway: I. Technique and Effects on Morphology, A. M. A. Arch. Ophth. 61:14, 1959.

2. Armaly, M. F.: Studies on Intraocular Effects of the Orbital Parasympathetics: II. Effect on Intraocular Pressure, A. M. A. Arch. Ophth. 62:117, 1959.

3. Armaly, M. F.: Effects of Electrical Stimulation of the Orbital Parasympathetic Pathway on Intraocular Pressure, Am. J. Ophth. 45:924, 1958.

4. Armaly, M. F.: Effect of Parasympathetic Stimulation on the Anterior Segment of the Cat's Eye, Tr. Am. Acad. Ophth., to be published.

5. Becker, B., and Constant, M. A.: The Facility of Aqueous Outflow, A. M. A. Arch. Ophth. 55: 305, 1956.

6. Bárány, E. H., and Scotchbrook, S.: Influence of Testicular Hyaluronidase on the Resistance to Flow Through the Angle of the Anterior Chamber, Acta physiol. scandinav. 30: 240, 1954.

7. Purnell, E. W.; Melton, C. E., and Adams, E. Q.: The Effects of Nerve Stimulation on Aqueous Outflow in Enucleated Eyes, Am. J. Ophth. 42:182 (Oct., Pt. 2) 1956.

Progressive Multifocal Leukoencephalopathy

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Astrom, Mancall, and Richardson[1] have recently directed attention to progressive multifocal leukoencephalopathy, a previously unrecognized neuropathological entity. Visual symptoms have been prominent in this disorder. As no cases have been reported in the ophthalmologic literature, the following instance of progressive multifocal leukoencephalopathy substantiated by biopsy is presented.

Report of Case

The patient was seen through the courtesy of Dr. Raymond D. Adams. This 57-year-old white right-handed male garage operator was admitted to the Massachusetts General Hospital for the first time on July 23, 1958, because of confusion and memory loss of three weeks' duration. But for some fatigability during the preceding two months, he had enjoyed perfect health. However, three weeks prior to admission, when he returned home from a trip in his wrecker, the patient was noted by his wife to be in a confused state, with no clear recollection of where he had been that afternoon. In the next day or two, a distinct personality change occurred. He became quieter and lacking in spontaneity, was slow in answering questions, and would sit with a blank expression on his face. A rapid deterioration of memory for recent events occurred, and he would become lost in familiar surroundings, such as his home and place of business. For these reasons, he stopped going to work and remained at home, although previously he had an excellent work record. During the next two weeks, he was noted to walk very cautiously and had a tendency to bump into things on his right. Although he retained his ability to write, he could not read, not even what he had just written. While forgetting recent events and being repetitious in his conversation and uncertain of day or date, his memory for the names of old acquaintances seemed unimpaired. Headache was denied. On occasion he mentioned terrible thoughts and frightening dreams but did not elaborate on the former and could not remember the content of the latter. The patient began to fear being alone, smoked more, and became very dependent on his wife. For these reasons, he was hospitalized. The history was otherwise negative.

On admission, general physical examination revealed a blood pressure of 130/80 and, but for slight prostatic hypertrophy, was within normal limits. Neurological examination revealed intact motor and sensory functions and normal deep tendon reflexes, and, but for the eyes, cranial nerves were intact. However, marked changes were revealed in the mental status examination. Although friendly and cooperative, with fluent speech and a good vocabulary, the patient was disoriented as to time and place. A profound and total alexia was present. He was unable to read even his own writing and at times could not identify even a single letter. Similarly, as he could not identify numbers, he was totally helpless in all written calculations. However, he could write his own thoughts, take dicta-

Submitted for publication May 4, 1959.

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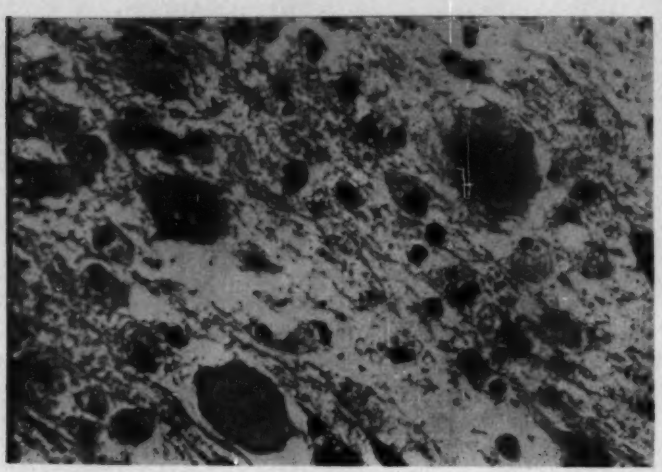
This study supported in part by Special Traineeship BT-357, National Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

tion, spell, and name objects well. No apraxia or agnosia were noted, and right-left confusion was not detected. A profound retentive memory defect was noted. The physicians could return to his room two or three minutes after an examination, and he could not recall having seen them that day. Yet during an examination his attention span was good.

Ophthalmologic examination revealed an interesting difficulty in obtaining the patient's vision. As he was totally unable to read letters from the chart, it was necessary to use the illiterate "E" test. It was difficult for him simply to point his finger in the direction of the "E," but finally he wase able to comprehend this, and 20/30 vision was detected in both eyes. External examination revealed normal lids, lacrimal apparatus, lashes, pupils, motility, and corneal reflexes. Convergence was present. There was no nystagmus. Bell's phenomenon was intact. Optokinetic nystagmus revealed slight asymmetry with a better response to targets to his right, but the optokinetic response was considered within normal limits. There was a complete and profound macular splitting right homonymous hemianopia. A modified Howard-Dohlman test as well as the Verhoeff stereopter revealed normal depth perception in the left fields. Color vision was intact, as he was able to trace the pattern on the AO pseudoisochromatic plates. Ophthalmoscopy revealed normal fundi, with spontaneous venous pulses seen in both eyes. Ophthalmodynamometry disclosed diastolic pressures of 22 units in both eyes (Bailliart). In summary, this 57-year-old white man was in good health until three weeks prior to entry, when he developed confusion, retentive memory defect, alexia, and right homonymous hemianopia. Examination revealed disorientation, altered mental status with confusion and retentive memory defect, a dense right homonymous hemianopia splitting fixation, and a normal optokinetic response to both sides. Examination was otherwise within normal limits.

Laboratory studies revealed hematocrit 48, hemoglobin 17.6 gm. %, sedimentation rate 7 mm. per hour, and white blood cell count 10,300. X-Rays of the abdomen revealed the liver edge to be somewhat prominent, the spleen was not seen, and no other abnormalities were seen. Skull x-rays were within normal limits. Lumbar puncture disclosed an opening pressure of 148 mm., 1 lymphocyte per cubic millimeter, protein 91 mg. %, and gold sol 0011100000. Arsenic scan and electroencephalography pointed to a left parietal lesion. Because of a clinical suspicion of an intracranial neoplasm, on July 30, 1958, a left temporo-parietal-occipital craniotomy was done with biopsy of abnormal brain.

The pathologic material was reviewed by Dr. E. P. Richardson Jr., who provided the following details: "The specimen of brain tissue removed at operation was fixed in formalin, and frozen and paraffin-embedded sections were prepared and stained with hematoxylin and eosin, cresyl violet, the Spielmeyer method for myelin, the Cajal method for axis cylinders, and with Sudan IV for neutral fat. These showed an extensive lesion of the white matter, consisting of almost complete loss of myelin sheaths. There was a narrow strip of relatively intact myelinated fibers in the region of the subcortical U-fibers. Although not entirely sharply defined, the border of the lesion was well demarcated. Axis cylinders were considerably reduced in number in the lesion, and many of those remaining were fragmented or showed irregular swellings and end bulbs. They were, however, relatively spared as compared with the myelin sheaths. The center of the lesion was filled with numerous macrophages containing brightly staining sudanophilic granules in the cytoplasm. At the periphery of the lesion were many large astrocytes, some of which had irregular hyperchromatic nuclei, while others were multinucleated. Along with these, there were considerable numbers of large, oval cells without definite processes, containing oriented blocks of



Giant astrocytes with mitotic figures.

chromatin suggestive of mitosis (Figure). Other cells of this type contained multiple tiny vesicular nuclei. There were frequent perivascular collections of lymphocytes in the adventitial spaces of small veins in the outer portions of the lesion. Although the border of the lesion in places encroached upon the deepest layers of the cortex, nerve cells were intact. The meninges were normal. These findings indicate a primary destructive disease of the white matter, with features characteristic of the demyelinative disorders. Although the available tissue was insufficient for full assessment of the pathological changes, the presence of numerous giant astrocytes, with what appear to be mitotic figures in some of these, are most suggestive of progressive multifocal leukoencephalopathy."

Dr. Raymond D. Adams reviewed the biopsy specimen findings and commented, "extensive loss of medullated fibers and large amounts of fatty maerophages containing cholesterol esters; giant astrocytes, some of which show mitotic figures; perivascular cuffing with lymphocytes. Cerebral cortex is spared. This group of pathological findings I have seen only twice or three times—in cases of multicentric focal demyelination in conjunction with leukemia, Hodgkin's disease, and once with sarcoid." Consequently a bone marrow aspiration was performed, which was reported as normal. Chest x-ray was within normal limits. One glucose tolerance test revealed a diabetic curve, but a repeat postprandial blood sugar on July 24, 1958, revealed 80 mg. % glucose.

Postoperatively the right homonymous hemianopia persisted, and for a few days there was an asymmetric optokinetic response (i. e., absent response with targets from the patient's right to his left, with an intact response to the other direction). However, this cleared and a normal response to both sides returned, as had been noted preoperatively. Mentally the patient continued to deteriorate. He became unable to perform the "E" game, and at discharge all that was known about vision was that he could count fingers at 15 ft. with each eye. Blinking was more frequent on the right than the left. On July 28, 1958, psychometric testing had revealed verbal intelligence as "average," while nonverbal ability and memory score were "defective." The patient had a slight wound infection which subsided on antibiotic therapy and was discharged to a nursing home on Aug. 16, 1958.

The patient was subsequently followed by Dr. Charles Knowlton, Ellsworth, Maine, who provided the following notes. Upon his return home, the patient was

able to get into a chair with help. He soon developed a right hemiparesis, beginning in the lower extremity and progressing to involve the upper extremity. Although he appeared to comprehend speech, he developed a progressive motor dysphasia. Gradual deterioration of vision occurred until the patient became entirely blind and would look toward the sound of a voice. Later difficulty in interpreting sound occurred, as he would not look in the proper direction of sound. Weakness then began in the left lower extremity and advanced to a complete left hemiplegia. Movements of the head, facial muscles, and eyes and swallowing remained intact until very late in the illness. Terminally dysphagia, progressive weakness, and circulatory collapse appeared. In the last days, the eyes appeared fixed in position with no muscular movements in the body except for slight ability to turn the head. The patient died quietly on Oct. 9, 1958. Postmortem examination was not obtained. The total duration of the illness was three and one-half months.

Comment

Astrom, Mancall, and Richardson[1] reported three cases of progressive multifocal leukoencephalopathy and stressed the relationship of this disorder to chronic lymphatic leukemia and Hodgkin's disease. In a review of the literature they found five similar cases. These authors were able to review the histology in three of the five additional cases and observed in each an identical process. Of the eight cases reported to date, there were three with Hodgkin's disease, two with chronic lymphatic leukemia, one with sarcoidosis, and one with pulmonary and renal tuberculosis; in one case no other lesion was apparent. Visual loss was recorded in six of these eight cases. The second case of Astrom et al. presented alexia and a right homonymous hemianopia, and their first patient had become blind. All of their patients had died between three and four months from onset.

They stressed the following clinical features: dementia, altered state of consciousness, language disorders, visual impairment, and evidence of pyramidal tract involvement. Cranial nerve palsies and sensory deficits were less common. Headache occurred in only one case, and seizures did not occur. The disease pursued a relentlessly progressive course. No significant abnormalities were found in the cerebrospinal fluid. The authors pointed out that, although this condition has been most frequently seen with a neoplastic disease of lymphatic tissue, such disorders are not required for its development.

The neuropathologic findings are of interest. The lesions are characterized by widely disseminated small perivascular foci of destruction of myelin sheaths with relative sparing of axis cylinders. Confluence of these foci may produce large plaque-like lesions. The most severely affected areas of the cerebral hemispheres are the posterior parts, although all levels of the brain could be involved. Associated with the demyelination was a distinctive cytologic reaction consisting of hypertrophy of astrocytes into bizarre gigantic forms, with mitoses, and alteration of oligodendrocytes with production of hitherto undescribed large round densely basophilic nuclei.

No specific form of therapy is available, and the cause of the condition is unknown.

A serious systemic illness has been apparent in the majority of previously reported cases, as noted above. It should be pointed out that, although there was no clinical evidence for such a disorder in the case here reported, in the last analysis a definite conclusion cannot be made in this regard, as postmortem examination was not obtained.

Summary

The ninth reported case of progressive multifocal leukoencephalopathy is presented. The patient was a 57-year-old man who

presented with confusion, retentive memory defect, alexia, and right homonymous hemianopia of three weeks' duration. A progressive neurological disorder, substantiated by cortical biopsy, caused death within four months from onset. Visual symptoms have been prominent in seven of the nine reported cases, and the attention of the ophthalmologist is directed to this disorder.

Acknowledgment is given to Dr. R. D. Adams, E. P. Richardson Jr., and Flavio Romanul for their help with this paper and to Dr. Charles Knowlton for notes on the terminal illness.

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REFERENCE

1. Astrom, K. E.; Mancall, E. L., and Richardson, E. P.: Progressive Multifocal Leuko-Encephalopathy, Brain 81:93, 1958.

Progressive Dystrophic External Ophthalmoplegia with Abiotrophic Fundus Changes

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The association of progressive external ophthalmoplegia and retinal degeneration, or "retinitis pigmentosa," has been noted in 13 previously reported cases.[1-4] This combination of ocular signs has been regarded as a syndrome of disease.[1-3] Recently a report of two patients with progressive paralysis of ocular movement with ptosis, retinal degeneration, and heart block was held to establish still a new syndrome.[5]

We have recently studied a patient who manifests these abnormalities, and we believe that the combination of symptoms is more properly regarded as a coincidence of abiotrophic manifestations rather than as a unique syndrome.

Progressive external ophthalmoplegia, although an uncommon disorder, has been a recognized clinical entity since von Graefe's original description.[6] The condition was usually regarded as secondary to nuclear degeneration[7,8] until recent definitive studies of the ocular muscles established primary myopathy as the cause of paralysis in most cases.[9-13] The ocular myopathy may or may not coexist with myopathy elsewhere and has been reported in patients displaying degenerative neuropathy.[14] While histologic examination of the ocular muscles provides the best evidence in differentiating the nature of an ophthalmoplegia in question, electromyography has proved to be a valuable adjunct in diagnosis.[15-17]

Retinitis pigmentosa, or pigmentary degeneration of the retina, is a specific disease entity that may be defined as to symptoms, signs, pathologic anatomy, and prognosis. Certain minimal clinical and laboratory findings must be present to make the diagnosis. It does not appear to be related to cases of so-called atypical "retinitis pigmentosa."

In the 13 cases of ophthalmoplegia and "retinitis pigmentosa" occurring together we noted the following:

1. Barnard and Scholz[1] presented the first four cases. In Case 1, ophthalmoplegia appeared after thyroid surgery. The ocular findings were very suggestive of retinitis pigmentosa. Cases 2 and 3 were Negroes, both were syphilitic, and neurological abnormalities other than ophthalmoplegia were present in one. The retinal changes as described were not those of retinitis pigmentosa, which is particularly rare in Negroes. Case 4 was a microcephalic adult who suffered several progressive neurological defects in addition to ophthalmoplegia and retinal degeneration. Again the presence of retinitis pigmentosa was in doubt.

2. Walsh[2] described five cases of ophthalmoplegia with atypical "retinitis pigmentosa" which he feels are proof that some cases of external ophthalmoplegia cannot be explained on the basis of a myopathy alone. In four of these cases (266, 267, 268, 277) the history was characteristic of ocular myopathy. There were no histologic studies.

3. Chamlin and Billet[3] described three cases as examples of atypical "pigmentary degeneration of the retina" associated with progressive external ophthalmoplegia. Cases 1 and 2 closely resembled those described by Walsh. In Case 3 bulbar palsy was evi-

Submitted for publication May 14, 1959.

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dent in addition to the principal findings. There were no tissue studies. We hesitate to agree with the authors that these cases represent neuroectodermal degeneration.

4. Erdbrink's [4] single case differed from most of the others in that the retinal affliction was well shown to be retinitis pigmentosa. The ophthalmoplegia was probably of myopathic origin.

5. In the two cases recently reported by Kearns and Sayre [5] "retinitis pigmentosa" and external ophthalmoplegia were associated with complete heart block. Case 1 was not shown to be retinitis pigmentosa, and Case 2 unequivocably was.

From this brief review it is evident that of these 15 patients certainly 2 and probably 3 had retinitis pigmentosa; 12 had other pigmentary changes in the retina, 2 possibly secondary to syphilis. Progressive external ophthalmoplegia was present in all, but the nature of the paralysis was established clearly only in one. Provided a specific etiological factor is not demonstrated, we feel that these diverse retinal degenerations with associated external ocular muscle paralyses are manifestations of more than one abiotrophy occurring in a single person.

The following case report exemplifies external ophthalmoplegia of myopathic origin associated with retinal degeneration, severe choroidal sclerosis, and heart block. The relationship of these findings in this patient will be discussed.

Report of Case

This 61-year-old white man was first seen at the Iowa City Veterans Administration Hospital on Aug. 4, 1958, because of pain in an amputation stump of the right leg. A below-the-knee amputation had been done on the right in 1951, because of gangrene of the foot attributed to arteriosclerosis. He had first noticed drooping of the eyelids bilaterally 12 years before and believed that it had been progressive since onset. Visual acuity had begun to diminish eight years before admission. The loss was progressive, with the right eye being more severely affected than the left. Symptoms of night blindness could not be elicited. No symptoms of cardiac disease were noted.

Physical examination revealed the patient to be alert, oriented, and somewhat garrulous. The blood pressure was 186/100 mm. Hg, the pulse was 72 per minute and irregular. Examination of the heart and lungs was not remarkable except for the cardiac irregularity. The abdominal organs were not palpable. Both testicles were atrophic. Femoral artery pulsations were weak in the left groin and absent in the right. The right leg had been amputated below the knee. There was stasis dermatitis of the left leg, and arterial pulsations were absent in this foot.

Marked ptosis with thinning of the upper eyelids was evident, as was inability to elevate the lids (Fig. 1). Externally both eyes were normal except for a senile arcus O. U. The pupils were 3/3 mm. round and equal and reacted promptly to light. The extraocular movements on both command and attempt to follow were nearly absent in all directions of gaze, and the eyes re-

Fig. 1.—Patient demonstrating bilateral ptosis.

mained constantly in the primary position. Bell's phenomenon was absent. The visual acuity of the right eye was limited to counting fingers at 3 ft. The acuity of the left eye was 20/25 (Snellen). On ophthalmoscopic examination the fundi were remarkably similar with the changes slightly more marked on the right. The discs were pale-appearing, with sharp margins, and were surrounded by wide areas of complete choroidal atrophy through which the sclera could be seen. In addition, there were several other areas of marked choroidal atrophy merging with areas of very conspicuous choroidal sclerosis. There was diffuse pigmentation, especially in the periphery, and the vessels were very attenuated peripherally.

In addition to ptosis, there was a general paucity of facial expression. Strength of neck flexion was reduced, but the strength in the upper and lower extremities was normal. There was no abnormality of the reflexes and no sensory deficit.

Laboratory Findings.—The hemoglobin was 14.4 gm. % and the white blood cell count was 8,200 per cubic millimeter, with a normal differential count. Sedimentation rate was 10 mm. per hour. Serologic test for syphilis was negative. The urine showed 1+ albumin but otherwise was normal. BUN and creatinine were 22.5 and 1.4 mg. %, respectively. Blood sugar was 130 mg. %. Sodium, potassium, cholesterol, and protein-bound iodine levels of the serum were all within normal limits. Examination of the spinal fluid revealed no abnormalities. Administration of edrophonium (Tensilon) had no effect on the ptosis or ocular rotations. Twenty-four-hour urine creatinine and creatine outputs were measured at 640 mg. and 214 mg., respectively; levels far below the accepted adult normal for creatinine and above the expected creatine output. Roentgenography of the chest revealed marked cardiac enlargement, while the electrocardiogram showed atrial fibrillation and an intraventricular conduction defect. The electroencephalogram was interpreted as abnormal with some excessive 7 per second θ-activity anteriorly.

Electromyography of the lateral rectus muscles revealed no evidence of fibrillation or obvious loss of motor units. There was abundant recruitment of the motor units on effort with marked decrease in voltage

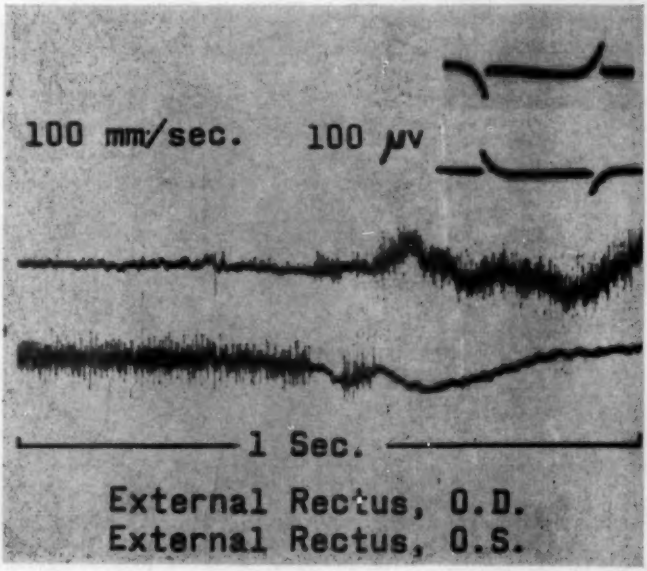

Fig. 2.—Simultaneous electromyographic tracing of right lateral rectus (above) and left lateral rectus (below) during attempted left to right gaze. Abundant recruitment, decreased voltage, and evidence of reciprocal innervation is seen.

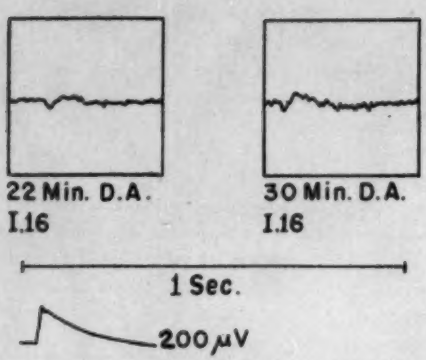

Fig. 3.—Electroretinogram with highest intensity stimulus, showing low *a*- and *b*-wave voltage.

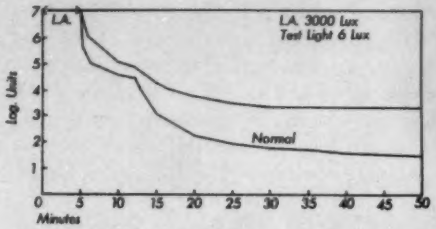

Fig. 4.—Dark-adaptation curve of patient (above) showing elevated rod and cone threshold. Normal curve (below) is plotted for comparison.

(Fig. 2). Simultaneous recordings of the right and left lateral rectus muscles made during attempted movement of the eyes showed a normal pattern of reciprocal innervation. It was felt that these findings provided evidence of an intact neural apparatus supplying the lateral rectus muscles.

Electroretinography was done on three separate occasions, and each time the result was the same. With none of the four intensities available with the Grass Photo-Stimulator could an ERG be elicited in the early stages of dark-adaptation. In the later stages an ERG was recorded with the highest intensity (I 16), but it was extremely subnormal. With this intensity both *a*- and *b*-waves were present; the *a*-wave measured approximately 40 microvolts after 22 and 30 minutes of dark-adaptation; the *b*-wave measured about 75 and 90 microvolts at 22 and 30 minutes, respectively (Fig. 3). This ERG is consistent with a considerable loss of rod and cone function but not characteristic of retinitis pigmentosa.

Dark-adaptation studies showed a markedly elevated cone and rod threshold (Fig. 4). This curve is believed consistent with severe damage to cone and rod function, especially the latter, but not consistent with retinitis pigmentosa.

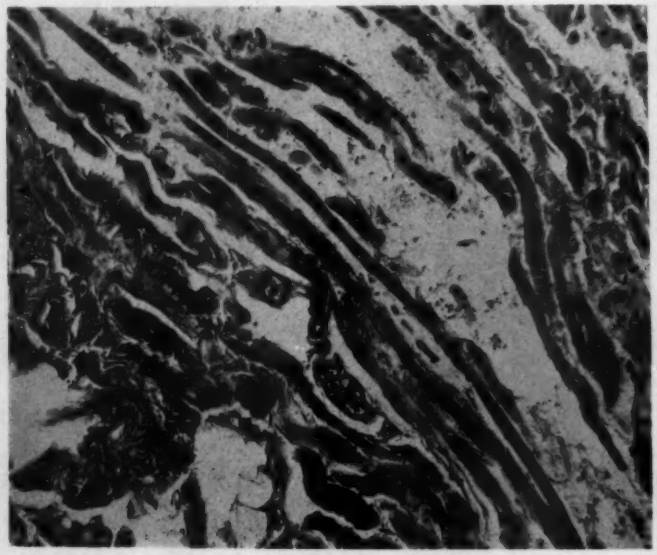

Fig. 5.—Biopsy specimen of right lateral rectus, stained with hematoxylin and eosin, showing characteristic dystrophic changes. Reduced ¼ from mag. × 600.

Fig. 6.—Muscle biopsy specimen, with Bodian stain, showing degenerating muscle fibers with intact terminal nerve element. Reduced ½ from mag. × 1,000.

A biopsy of the lateral rectus muscle was obtained and stained by the hematoxylin and eosin and Bodian techniques. With hematoxylin and eosin the muscle showed the characteristic findings of a dystrophic process (Fig. 5). Marked variation in the size of the muscle fibers with alterations in staining characteristics was evident. Degenerating muscle fibers were separated by an increase in connective tissue elements and fatty tissue. An increase in sarcolemmal nuclei also was observed. The Bodian stain showed intact nerve elements and nerve endings among the dystrophic muscle fibers (Fig. 6).

Diagnoses were (1) dystrophic external ophthalmoplegia, (2) retinal degeneration, (3) choroidal atrophy and sclerosis, (4) cardiac conduction defect, and (5) peripheral arteriosclerotic vascular disease, with amputation of the right leg.

Comment

We believe that this patient suffered from the manifestations of contemporaneous abiotrophic processes. Both mesodermal and ectodermal structures are involved. The retinal degenerative changes have been shown not to be retinitis pigmentosa as evidenced by history, fundus examination, electroretinography, and dark-adaptation studies. The ptosis and ophthalmoplegia are the result of a primary myopathy of the extraocular muscles. The low urine creatinine and elevated urine creatine, the characteristic electromyographic changes, and the histologic findings are ample proof of this. Degeneration of mesodermal tissue is evidenced by the marked choroidal alterations. The cardiac conduction defect cannot be claimed to be associated with a primary myopathy from the data obtainable.

Gowers [18] coined the term abiotrophy to designate a degenerative process resulting from an essential failure of vitality. Collins [19] stated that abiotrophy is a justifiable classification of disease for those pathologic processes that are hereditary, bilateral, show no evidence of inflammation, and on pathologic examination reveal cells which having reached a full degree of development and functional efficiency have then undergone degeneration. Cogan [20] agreed that abiotrophies are as well defined as infections, neoplasms, and allergies. He stated that the characteristic features are the extraordinary specificity for one particular tissue, the bilaterality and approximate symmetry, the spontaneous occurrence in a tissue having normal function with ultimate complete annihilation of this function, and the tendency to occur in families.

Designating the above-reviewed and reported cases as examples of multiple abiotrophies rather than looking upon them as representing a syndrome has several advantages. The simultaneous occurrence of progressive defects involving embryologi-

cally diverse tissue types can be more readily explained. The prognosis of abiotrophies can be fairly accurately ascertained with respect to loss of function of the organ system or tissue involved. We know that therapy other than symptomatic treatment is not at present available. Finally the concept of abiotrophy may turn our attention to the more basic idea of cellular or molecular disease and guide our search for etiology, pathogenesis, and treatment along more fruitful paths.

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REFERENCES

1. Barnard, R. I., and Scholz, R. O.: Ophthalmoplegia and Retinal Degeneration, Am. J. Ophth. 27:621-624, 1944.

2. Walsh, F. B.: Clinical Neuro-Ophthalmology, Ed. 2, Baltimore, The Williams & Wilkins Company, 1957, pp. 644-646.

3. Chamlin, M., and Billet, E.: Ophthalmoplegia and Pigmentary Degeneration of the Retina, Arch. Ophth. 43:217-223, 1950.

4. Erdbrink, W. L.: Ocular Myopathy Associated with Retinitis Pigmentosa, A. M. A. Arch. Ophth. 57:335-338, 1957.

5. Kearns, T. P., and Sayre, G. P.: Retinitis Pigmentosa, External Ophthalmoplegia, and Complete Heart Block, A. M. A. Arch. Ophth. 60:280-289, 1958.

6. von Graefe: Verhandlungen arztlicher Gesellschaften, Berlin, Berliner Klinische Wochenschrift, 1868, p. 127.

7. Walsh,[3] p. 236.

8. Langdon, H. M., and Cadwalader, W. B.: Chronic Progressive External Ophthalmoplegia: Report of Case with Necropsy, Brain 51:321-333, 1928.

9. Sandifer, P. H.: Chronic Progressive Ophthalmoplegia of Myopathic Origin, J. Neurol. Neurosurg. & Psychiat. 9:81-83, 1946.

10. Kiloh, L. G., and Nevin, S.: Progressive Dystrophy of the External Ocular Muscles (Ocular Myopathy), Brain 74:115-143, 1951.

11. Schwarz, G. A., and Liu, C-N.: Chronic Progressive External Ophthalmoplegia: A Clinical and Neuropathologic Report, A. M. A. Arch. Neurol. & Psychiat. 71:31-53, 1954.

12. Kirschbaum, W. R., and Holland, J. J.: Progressive Dystrophy of the External Eye Muscles, Neurology 8:304-306, 1958.

13. Nicolaissen, B., and Brodal, A.: Chronic Progressive External Ophthalmoplegia A. M. A. Arch. Ophth. 61:202-210, 1959.

14. Stephens, J.; Hoover, M. L., and Denst, J.: On Familial Ataxia, Neural Amyotrophy, and Their Association with Progressive External Ophthalmoplegia, Brain 81:556-566, 1958.

15. Breinin, G. M.: Electromyography—A Tool in Ocular and Neurologic Diagnosis, A. M. A. Arch. Ophth. 57:161-175, 1957.

16. Breinin, G. M.: New Aspects of Ophthalmoneurologic Diagnosis, A. M. A. Arch. Ophth. 58:375-388, 1957.

17. Blodi, F. C., and Van Allen, M. W.: Electromyographic Studies in Some Neuro-Ophthalmologic Disorders: I. Progressive External Ophthalmoplegia, Transactions of the XVIII International Ophthalmological Congress, Brussels, Sept. 11, 1958, to be published.

18. Gowers, W. R.: A Lecture on Abiotrophy, Lancet 1:1003-1007, 1902.

19. Collins, E. T.: Hereditary Ocular Degenerations: Ophthalmic Abiotrophies, in Proceedings of An International Congress of Ophthalmology, Washington, D. C., 1922, pp. 103-143.

20. Cogan, D. G.: Neurology of the Ocular Muscles, Ed. 2, Springfield, Ill., Charles C Thomas Publisher, 1956, pp. 41-44.

Ocular Rigidity

A Clinical Study

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Ocular rigidity was measured in a total of 560 routine office patients with use of Friedenwald's tonometric method of paired weights in conjunction with his 1955 tables. Patients were discarded from consideration when inadequate cooperation prevented a measurement free of lid squeezing or ocular movement. Tonometric measurements lower than 3 or higher than 12 on the scale were also discarded. Contrary to my own expectations I found that children could often be readily examined.

Presently there appears to be a difference of opinion as to whether the coefficient of ocular rigidity as formulated by Friedenwald [1] is in actuality a constant for the individual eye. The tables of intraocular pressure for the indentation tonometer as well as the procedure of tonography are based in part on the concept of an average ocular rigidity of 0.0215, constant in each eye under all circumstances of intraocular pressure. If the coefficient is found not to be a constant the pressure tables in use now must be altered.

Perkins and Gloster [2] found in rabbits and Macri [3] et al. found in cats that the coefficient of rigidity increased as the intraocular pressure was increased. McBain,[4] who worked with enucleated human eyes, as did Gloster and Perkins,[5] found, on the other hand, that the rigidity varied inversely as the intraocular pressure. McDonald,[6] in living human eyes, also found an inverse relationship of the two factors.

The present study attempts to arrive at a relationship between intraocular pressure and ocular rigidity. In addition, the influence of the following factors is considered: age, state of refraction, depth of anterior chamber, estimated intraocular pressure by finger palpation, and surgical aphakia.

Emphasis should be placed on the fact that tonometric examination is in no sense so accurate a procedure that wide conclusions are to be drawn on the basis of one reading, or even a few. The errors inherent in this procedure are well known, and indeed are becoming better understood, but are disturbingly obvious in the course of a study such as this. Attempts at repeated examination in the same patient at subsequent dates produced such a confusion of results that it was considered best to obtain an average of a large enough number of patients in each category. Even where the patient was apparently at ease and not evidencing blepharospasm or ocular movement, occasionally one met with such wide excursions of the tonometer pointer that spasm of the extraocular muscle could be presumed. These patients were of course excluded from the study.

Age and Refractive Error

Table 1 shows in the 0 to +5.00 refraction group a generally higher level of coefficient of rigidity with increasing age, as well as a generally higher coefficient in the 0 to +5.00 refraction group as compared to the −0.25 to −6.00 group in the 5 to 20 and in the above 60 age group. One of the purposes of this study was to determine whether ocular rigidity was lower in the myope than in the hyperope in accordance with the idea that onset and pro-

Submitted for publication May 21, 1959.

From the Department of Ophthalmology, Montefiore Hospital.

TABLE 1.—*Ocular Rigidity by Age and Refraction*

Age	Mean Ocular Rigidity *	
	0–+5.00	—25–—6.00
5-15	0.0177 (65)	0.0147 (88) †
15-20	0.0158 (43)	0.0124 (75) †
20-30	0.0173 (42)	0.0166 (51)
30-40	0.0186 (30)	0.0183 (32)
40-60	0.0191 (201)	0.0182 (76)
60+	0.0201 (123)	0.0165 (26) †
All ages	0.0187 (504)	0.0157 (348) †

* Numbers in parentheses indicate number of eyes.
† Difference is significant at 0.01 probability level.

gression of myopia may have something to do with increased scleral distensibility. Some evidence in favor of this idea was found in the lower coefficient of rigidity in the 5 to 15 age group and 15 to 20 age group.

Depth of Anterior Chamber

In 16 eyes with shallow chambers, the coefficient of rigidity was 0.0227 and the intraocular pressure was 20.6. In 32 eyes with deep chambers, the coefficient of rigidity was 0.0183 and the average intraocular pressure was 20.1. This difference in rigidity is statistically significant. Francois et al. pointed out the influence of the depth of the anterior chamber on the facility of outflow and showed that irrespective of intraocular pressure the facility was greater in the eyes with deep anterior chambers. The assumption that increased ocular rigidity in eyes with shallow anterior chambers has to do with lower facility of outflow must for the present be kept open. It would be interesting and possibly rewarding to compare a series of eyes with differing facilities of outflow with regard to their coefficient of ocular rigidity.

Finger Palpation

Finger palpation as a method of determining intraocular pressure is notoriously inaccurate. It occurred to me that possibly differences in ocular rigidity could be responsible for some of the mistaken impressions we get from finger palpation. Patients over 40 years of age were selected for this part of the study, since in younger age groups bias on the part of the examiner would favor inclusion of more patients in the normal finger-palpation group. Patients were classified as to whether tension was clearly normal or possibly elevated. In 51 eyes with definitely normal finger tension the average intraocular pressure was 18.1 and the coefficient of rigidity was 0.0180, while in 82 eyes whose finger tension was questionably elevated the average pressure was 21.4 and the average coefficient of rigidity was 0.0190. Ocular rigidity obviously had no relation to the impression one gained from finger palpation.

Surgical Aphakia

An attempt was made to determine the effect of cataract extraction on ocular rigidity. In 23 eyes which had had cataract extractions the intraocular pressure was 21.0 and coefficient of rigidity was 0.0163. In the 23 fellow eyes the intraocular pressure was 21.7 and coefficient was 0.0174.

Intraocular Pressure

The 40 to 60 age group having refraction of 0 to +5.00 was large enough in numbers to warrant classifying each eye on the basis of intraocular pressure. Table 2 indicates that in each age group the coefficient varied inversely as the intraocular pressure. This finding is in accordance with

TABLE 2.—*Ocular Rigidity and Intraocular Pressure in Patients Age Forty to Sixty*

Intraocular Pressure	Mean Ocular Rigidity *	
	0–+5.00	—25 & Up
—15.0	0.0288 (14)	0.0220 (7)
15.0-19.9	0.0205 † (80)	0.0193 (27)
20.0-24.9	0.0173 † (82)	0.0165 † (54)
25.0+	0.0158 (24)	0.0139 † (14)
Total	0.0191 (201)	0.0173 (102)

* Numbers in parentheses indicate number of eyes.
† Difference is significant at 0.05 probability level or less.

TABLE 3.—*Comparison of Mean Intraocular Pressure with Mean Ocular Rigidity*

	Mean Intraocular Pressure	Mean Ocular Rigidity
Anterior chamber		
Shallow	20.6	0.0229
Deep	20.1	0.0183 *
Finger tension		
Minus	18.1	0.0180
Plus	21.4	0.0190
Cataract extraction		
Surgical aphakia	21.0	0.0163
Fellow eye	21.7	0.0174

* Difference is significant at 0.1 probability level.

those of McBain, Gloster and Perkins, and McDonald. The coefficient of ocular rigidity would therefore appear to be a function of intraocular pressure.

Summary

A group of 560 patients was studied by Friedenwald's two-weight method, deriving for each eye the coefficient of ocular rigidity.

The coefficient seemed to increase with age after the age of 20 and was significantly higher in the hyperope than in the myope, in the 5 to 20 and 60+ age groups.

The coefficient of ocular rigidity was higher in eyes with shallow anterior chambers than in those with deep ones.

The method of finger palpation to derive intraocular pressure owed none of its inaccuracies to ocular rigidity.

The operation of cataract extraction produced no change in ocular rigidity.

The coefficient of ocular rigidity varied inversely with intraocular pressure in a large group of cases.

Dr. Samuel Gartner, Director of the Eye Service, Montefiore Hospital, and Mr. Abe Siegelaub, Statistician of Montefiore Hospital, aided in the preparation of this paper.

1777 Grand Concourse (53).

REFERENCES

1. Friedenwald, J. S.: Contribution to the Theory and Practice of Tonometry, Am. J. Ophth. 20: 985-1024, 1937.

2. Perkins, E. S. and Gloster, J.: Distensibility of the Eye, Brit. J. Ophth. 41:93-102, 1957.

3. Macri, F. J.; Wanko, T.; Grimes, P. A., and von Sallmann, L.: The Elasticity of the Eye, A.M.A. Arch. Ophth. 58:513-519, 1957.

4. McBain, E. H., in discussion on Tonometry, Am. J. Ophth. 47:563-564 (Jan., Pt. 2) 1959.

5. Gloster, J., and Perkins, E. S.: Distensibility of Human Eye, Brit. J. Ophth. 43:97-101, 1959.

6. MacDonald, R. K.: Symposium on the Clinical Assessment of Glaucoma with Particular Reference to Diurnal Variations in Pressure: Observations and Interpretations, Tr. Canad. Ophth. Soc. 7:178-184, 1955.

7. Francois, J; Rabaey, M.; Neetens, A., and Evens, L.: Further Perfusion Studies on Outflow of Aqueous Humor in Human Eyes, A.M.A. Arch. Ophth. 59:683-691, 1958.

Inheritance of Retinoblastoma in Ohio

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Retinoblastoma is a relatively rare disease, and one which is fraught with tragedy for both parents and patients. A study was made on the population of Ohio on the following points: (1) Did the mode of inheritance as exhibited in Ohio families confirm the findings of other workers that the disease was caused by a dominant incompletely penetrant gene? (2) What estimate could be made of the degree of penetrance? (3) What was the estimate of the mutation rate of the normal gene to one for retinoblastoma? (4) What was the frequency of the disease among the births in Ohio?

Material for the Study

The names of all the children who had been born in 1940 through 1956, and who had developed retinoblastoma by the end of 1958 were asked for, the requests being sent (1) to all registered ophthalmologists in Ohio, (2) to all hospitals apart from mental and tuberculosis hospitals in the state, (3) to the Columbus State School for the Blind, and (4) to the Ohio Services for the Blind. In addition, all death certificates for children dying with retinoblastoma in Ohio were searched for those years. Some of the children whose names were received were not born in Ohio, and could not be used for questions 3 and 4 asked above, although they could be used in the general study. Many of the names were duplicates, and were found by a number of the methods just outlined. No claim is made that *all* children affected in these years were found, but it is felt that the ascertainment was rather complete. Only those on whom a pathological diagnosis was made were accepted.

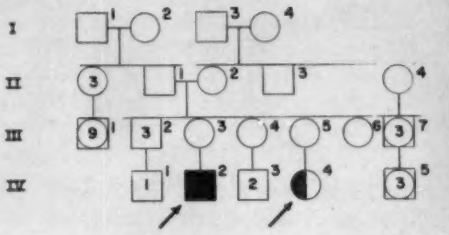

Fig. 1.—The probands are first cousins, children of two sisters. The number of relatives of the affected girl who have been fully traced are 8 great-grandparents, 4 grandparents, 14 great aunts and uncles on both sides of the family, 25 of their children, 10 of their grandchildren, the 2 parents and their sibs, also first cousins. The paternal side of the male proband was not traced, since the gene appeared to be coming through the two mothers. The fathers of the probands were not related to their wives or to each other.

In all cases, squares are males, circles are females. Completely black symbols represent bilateral involvement, half black symbols unilateral cases. The figures do not represent the number of relatives traced, but are a skeleton outline designed mostly to show the latest generation in which the mutation could have occurred to be reproduced in the affected relatives.

There were 119 names of children, who, after the most extensive investigation of the family history which was possible, were classed as sporadic cases, since no other relatives were found who had the same disease. The names of other relatives included all eight great-grandparents and all their descendants as far down the line of descent as was necessary to go to arrive at children too young to have had families of their own. The names, birth dates, and death dates when the relatives were deceased were secured. All death certificates for these relatives were looked for in Ohio

Submitted for publication June 4, 1959.

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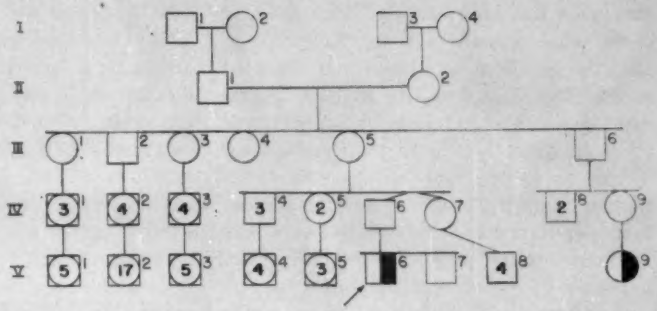


Fig. 2.—The family of the proband *V 6* has been traced, but only the father's maternal side is shown in the figure, since it was this line that carried the gene. The total relatives traced on the side of *IV 6* were 4 great-grandparents, 2 grandparents, 11 great aunts and uncles and their 71 descendants. On the side of the mother of *V 6* not shown in the figure, the 4 great-grandparents, 2 grandparents, 4 great aunts and uncles, and their 16 descendants were traced. The paternal side of *V 9* was not traced, but no eye cancer was reported by the family.

and other states. All living relatives except small children were written to for information on themselves, their parents, their sibs and their children, as well as for more remote relatives. For the latter, addresses were secured, so that they in turn could be written to for confirmatory or corrective statements received from others in the kinship. This was continued until all possible information was secured on all relatives who were descendants of the great-grandparents. Each person was asked if they knew of any case of eye cancer in any relatives besides the index case. Where possible, relatives even more remotely related were investigated.

This continued checking into the family history succeeded in placing two separate index cases into the same pedigree four times, once as first cousins (Fig. 1), once as second cousins (Fig. 2) (here neither parent knew of the disease in the other index case); once as second cousins once removed (Fig. 3) and again, neither set of parents was aware that the disease existed in a relative, and once as third cousins once removed (Fig. 4 *V 5* and *VI 1*, the latter being also an index case). Figure 5 shows the same two index cases related through another ancestor, this time as fourth cousins once removed (*V 7* and *VI 1*). It also showed in other pedigrees

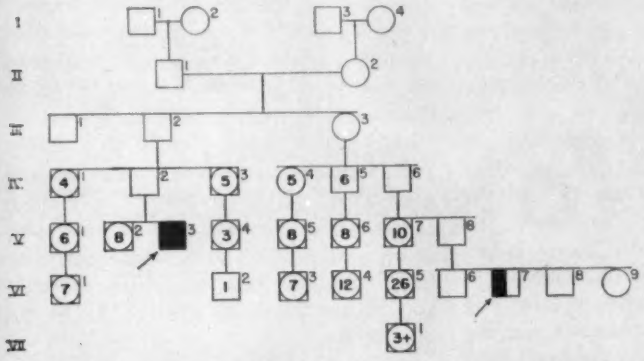


Fig. 3.—The skeleton outline of the common relatives of *V 3* and *VI 7* are shown. Neither family knew of the existence of the other affected child. In addition to the relatives shown on the right side of the figure, the wife of *IV 6*, her parents, her one sister, and the sister's two children were traced. On the side of the mother of *VI 7*, not shown in the figure, four great-grandparents, two grandparents, six great aunts and uncles, their nine descendants, the mother, her three sibs and their three children were traced, and all were free of retinoblastoma.

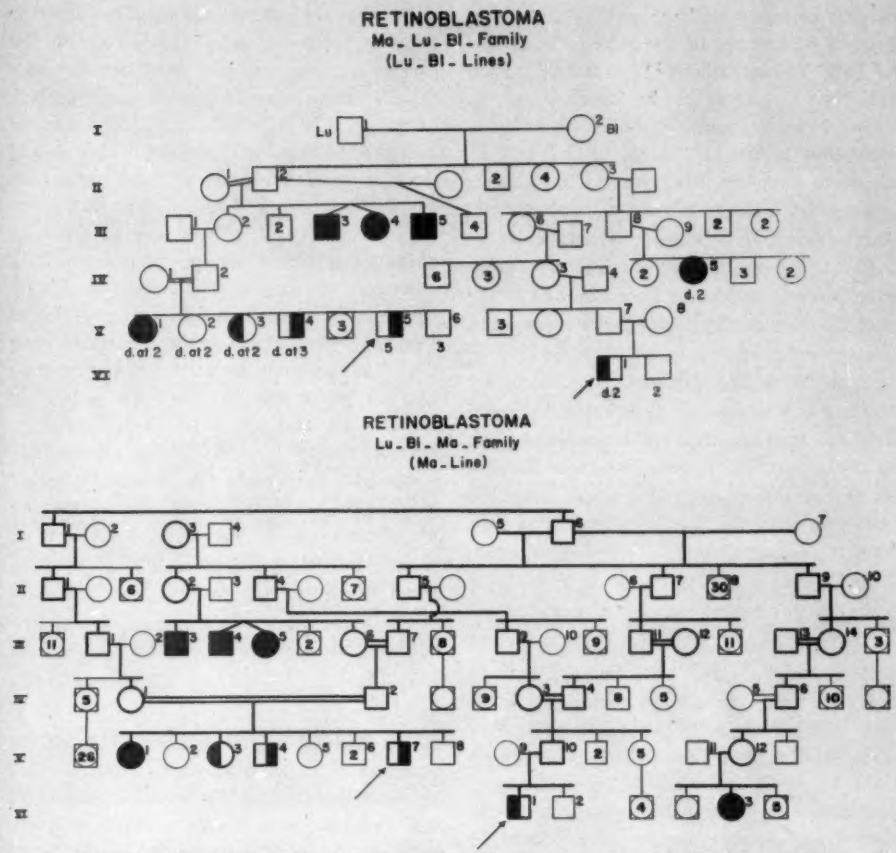
The paternal side of the family of *V 3* is shown; *II 1* and *II 2* were traced, but none of the family of the wife of *III 2*, who is not in the figure, were found. *III 1* died in Germany; nothing is known of him or his descendants. The relatives of the mother of *V 3* were traced. They were 4 great grandparents of the proband, 2 grandparents, 21 great aunts and uncles, and 88 of their descendants, with an unknown number of the latest generation not found. The mother was one of 14 children, 6 of whom died young, nothing known of them, but not thought to have had eye cancer. Her sibs had 25 children, none with retinoblastoma.

that what had been considered as sporadic cases were actually not so, but were in families in which a relative not reported as an index case was also affected. Again the families had not been aware of these other existing cases until the investigation carried on in this study revealed them. In Figure 6, a third cousin once removed was found in Kentucky, although this case was not known to the parents of the index case. Similarly in Figure 4, *IV 5* was found as a second cousin once removed to the index case *V 5*, and as first cousin twice removed to the index case *VI 1*. These relationships were unknown to the parents of the affected children. These same two children are related to each other as fourth cousins through another line.

In other families, other cases were also found in collateral lines and were unknown to the parents of the index case. In Figure 7, the father's maternal uncle had died at the age of two with retinoblastoma. The father of the index case had died years before and the mother had remarried. When interviewed she knew of no case in her first husband's family. In Figure 8, the second case is not a verified one, since no death certificate was found, and the physician treating the case was dead. But *IV 2* in the pedigree reported that her first cousin had died at an early age with tumors of the eyes, which made them bulge out and hang down over his cheeks. He had had no operation. Finally, in Figure 9, a brother of one of the great-grandfathers had had cancer of the eye at an early age according to the family Bible and had died of the disease. In Figure 10, the mother of the index case did know of the disease in her cousin's child. The affected male, *V 9*, marked with a cross hatched square, was reported as having retinoblastoma, but the pathological diagnosis was secured, and found to be glioma of the pons.

Mode of Inheritance

There is a large proportion of families in this study, as in all studies of this disease, in which the cases are isolated ones. This would suggest that the gene for the disease is a recessive. Even in those families in which *sibs* are affected, the parents are normal (Figs. 4, 11, 12, 13, 14). In only two families a parent of the index case was affected also (Figs. 14, 15). In both these families, only one child of the affected parent was affected, however. The objection to the interpretation that the gene is recessive is the low frequency of consanguineous matings between parents of the affected children. The disease is a rare one, occurring approximately once in every 23,287 persons born who lived past the age of one year in the 17 years under investigation in Ohio. This would mean that about 9% to 10% of the marriages producing children with retinoblastoma should be between first cousins. In only two marriages out of a total of 140 producing affected children were they between relatives, and in none were the parents as close as first cousins. These two marriages are between *IV 1* and *2*, who are third cousins in Figure 5, and between *II 2* and *3* not shown to be related through the Ma line in Figure 5, but are shown to be related through the St line in Figure 4; they are *II 1* and *2*. It was found out later that they were first cousins once removed. The family shown in Figures 4 and 5 comes from an isolated section of Kentucky, where a very high proportion of marriages are between relatives of some degree. Over 4,000 persons have been traced in this family, related to the four lines producing the affected offspring, and dozens of related marriages have been found, although these are the only two which produced children with retinoblastoma. The fact that consanguineous matings are not significantly higher than in the general population would be definitely opposed to the idea that retinoblastoma is caused by a recessive gene. The frequency with which it affects children of both sexes, and the fact that when parents marry, who are not sporadic cases as in Figures 14 and 15, some of their children were affected



Figs. 4 and 5.—These relate to the same four affected related sibships. All affected children were descended from the same four families, the *Lu*, the *Bl*, the *St*, and the *Ma* lines. *II 1* and *II 2* are related through his mother, *II 1* being the first cousin to *I 2*. *VI 1* is also a proband. Only by tracing back for four generations in Figure 4 was it shown that *VI 2* belonged in the pedigree with the other three sibships. Figure 5 shows the relationships through the *Ma* line. Related marriages in the *Ma* family are shown with double mating lines; *V 1-8* are descended from the *Ma* brother through their mother, from an *Ma* woman, presumably the sister of *I 1* and *I 6*, through their father and from another *Ma* brother again through their father. Traced through the *Ma* line, *VI 1* and *3* are in the same generation, but traced through the *Lu*, the *Bl*, or the *St* lines they are two generations apart. Over 4,000 relatives of these affected sibships have been traced, without finding other cases of retinoblastoma. The mother of *I 2* (Fig. 4) was in the *St* line, the father of *I 2* being in the *Bl* line.

support the interpretation of a dominant gene with incomplete penetrance.

Penetrance

What degree of penetrance does the gene exhibit in those families in which the penetrance can be estimated? Unless one regards the condition as dependent upon more than one gene, or unless one assumes that there may be several types of retinoblastoma dependent either upon different genes, or upon genetic factors in some cases, and upon environmental factors in others, the apparently hereditary cases offer some opportunity of estimating the degree of penetrance.

It is at this point that these families do not fit into the picture as portrayed by

other workers who have estimated the degree of penetrance of the gene to be as low as 78% (Franceschetti[1]) to 98.5% (Falls and Neel[2]). Some of the families such as those represented in Figures 4 (the sibship with four affected) 11, 12, 13, 14, and 15 do show complete penetrance if the gene is interpreted as a dominant, once it has become evident in a sibship. It cannot show complete penetrance in these families, however, since it had to be nonpenetrant in the normal parents, and sometimes even in a grandparent before it became evident in sibs or in related families. On the other hand, a low degree of penetrance is found in these families, ranging from about 20% to 30%, if all collateral lines are thought of as being the result of a single mutation in some previous generation, which then had to descend through a number of unaffected persons before becoming evident as the disease. It also had to be nonpenetrant in many of the sibs of the carriers of the gene, because half of the germ cells of a carrier parent should also carry the gene, and result in a carrier who in turn could transmit the gene to his descendants.

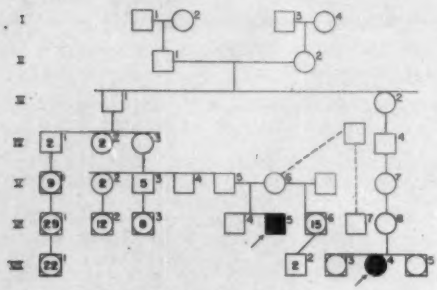


Fig. 6.—The Ohio proband, *VI 5*, was the 18th child of his mother, the second of his father. A second proband in Kentucky, *VII 4*, was shown to be related to *VI 5*. The maternal side of *VI 5* is not shown in the figure, but the 4 great-grandparents, 2 grandparents, 6 great aunts and uncles, their 47 descendants, the mother, her 7 brothers and sisters and their 21 children were all traced; none were affected. In addition to the relatives of *IV 3* shown here, the relatives of *V 4*'s father are not shown, but were traced. They were related to *VI 5* as follows: 2 great-grandparents, 1 grandparent, 7 great aunts and uncles, their 27 children, and their 48 grandchildren; all were free of retinoblastoma.

If one regards the possibility that the gene may have a semilethal effect on the carrier zygote, one can interpret the lack of affected persons in a sibship not as lack of penetrance, but as failure of many of the affected zygotes to develop. This would explain such sibships as those found in Figure 3, where *V 3* was one in nine to be affected, where *IV 2* was one in ten who appeared to carry the gene, and similarly where *IV 6* was one in twelve, and *V 8* was one in eleven who were carriers. On the other hand, many of the zygotes bearing the gene do come to birth, and may even live for years later, as have the fathers in Figures 14 and 15. The carrier may be one of a very large family as in the sibships just cited, and the interpretation of a semilethal calls for an exorbitant number of pregnancies to begin, in order that so many affected zygotes will be lost and still leave 11 or 12 normal ones to develop.

Mutation Rate

Before one can discuss the mutation rate several points have to be clarified. First, those cases in which sibs or a parent, or collateral lines were affected cannot be used in the estimation of the mutation rate since the mutation must have occurred in germ cells not giving rise to births in the years under study. Second, cases not born in Ohio must be excluded. Third, it is possible that not all the sporadic cases represent mutations in the germ cells. It is conceivable that some of the unilateral cases are caused by mutations in the somatic cells of one eye. That two such mutations should arise in the cells of the two eyes in one person is most improbable so that sporadic bilateral cases would be likely to be germinal in origin rather than somatic. Finally, it is possible that either uni- or bilateral sporadic cases are caused by some environmental situation and are, therefore, to be regarded as phenocopies. Neither the somatic mutational type nor the phenocopies will transmit the defect to their offspring. Unfortunately, it is not possible in any

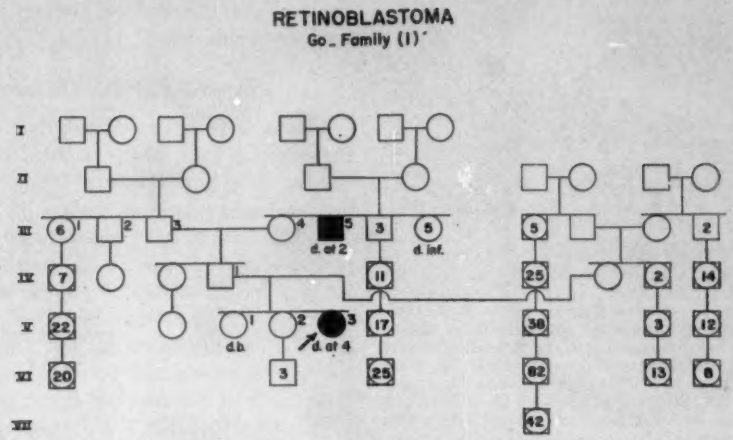


Fig. 7.—The proband *V 4* died at the age of four. Her father *IV 1* had died many years before. The mother had remarried. Her family is shown on the right side of the figure, with all relatives normal. The case was classified as sporadic, until a brother of the paternal grandmother was found who had the family Bible. *III 5* was listed in it as having died after removal of his eyes for eye cancer. This may not be a case of true retinoblastoma.

given case, where the disease appears as an isolated instance in the family, to state whether it is caused by a germinal mutation, hence to be counted as one for the estimation of the mutation rate, or whether it is caused by somatic mutation, or is a phenocopy. Fourth, some unilateral cases

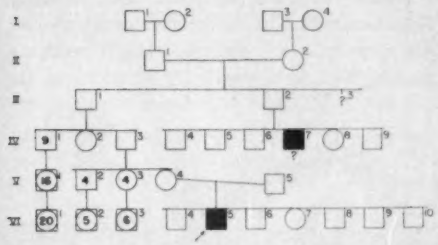


Fig. 8.—This represents another questionable case, since no diagnosis was obtainable, although the male *III 7* was stated by members of the family to have died at the age of two with bilateral eye cancer. The relatives of *VI 5* on the paternal side, and not shown, were 4 great-grandparents, 2 grandparents, 22 great aunts and uncles, 17 of them and their descendants untraced in Europe, 20 descendants of the other 5, the father, his 3 sibs and their 10 children. Apart from the 17 unknowns, all were traced and were normal. In addition to the relatives of *IV 3* shown in the figure, his wife, her two parents, her 11 sibs, their 32 children, their 81 grandchildren, their 126 great-grandchildren, her child, and the mother, who is *V 4*, have been traced, and all were normal. The questionable case is a first cousin of the maternal grandfather of the patient.

may die before they have a chance to exhibit the disease in the other eye, although it was destined to appear in the second eye if the child lived. Fifth, unilateral cases have survived, and produced children with the disease in bilateral form (Fig. 14), thus proving the hereditary nature of that unilateral case. Sixth, the low degree of penetrance found to exist in these families makes it very possible that many instances of true hereditary cases failing to transmit to their offspring could occur, giving the false appearance of a somatic mutation or a phenocopy in the parent. These various factors make it unwise to offer any hard and fast statement as to the mutation rate of retinoblastoma.

Certain estimates are possible, however. One can count all cases that gave evidence of being isolated instances in the family as examples of true mutation, or one can count only the bilateral sporadic cases. This would give an upper and lower limit to the possible mutation rate. Since bilateral cases are significantly more frequent among the proved hereditary cases (58.8% in this study) than they are among the isolated instances (31.6%), the use of bilateral cases only might insure one against includ-

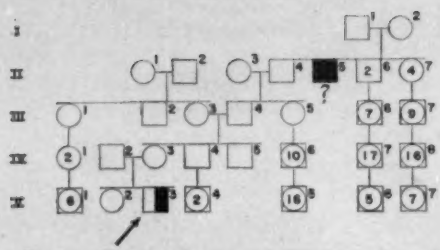


Fig. 9.—The family line of *IV 3*, mother of the proband, is shown in the pedigree, with the unconfirmed case present in *II 5*. The family of the father, *IV 2*, was also traced, with the following relatives accounted for and all normal as far as retinoblastoma was concerned. There were 4 great-grandparents, 2 grandparents, 10 great aunts and uncles, their 16 children, 43 grandchildren and 12 great grandchildren, 6 uncles, 8 first cousins and 2 children of one of them, who were all normal.

ing any that were not hereditary, but would leave one open to the error of leaving out some that were. Using these two sets of figures, the mutation rate in Ohio for the 17 years under study proved to be 1.76×10^{-5} when all sporadic cases were included, and 0.63×10^{-5} when only bilateral cases were included. The true rate probably lies somewhere between. Mutation rates for white and Negro were computed separately; the rate for the Negro proved to be higher. This was the reverse of what Falls and Neel[2,3] found in Michigan, but in both series the numbers were small, so that the opposite findings probably have no significance.

Frequency of the Disease

This is a different estimate than that for the mutation rate, which is based upon the number of genes while the frequency estimate is based upon the number of persons. Thus for every 100 persons born in any period of time, there are 200 genes present for any locus not carried on the sex chromosomes. Hence, the mutation rate is based upon the ratio of the number of sporadic cases who are born within a given time, to twice the number of persons born in that same period. The frequency of the disease is based upon the ratio of affected persons (hence, including the hereditary as well as sporadic cases) born within a given time to the number of births occurring in that same period. In this study this was about 1 in 23,287 persons who survived to the age of one year.

Risk of Producing Affected Offspring

This risk concerns three different types of people. The first is a victim of this disease who knows that others of his sibs, or a parent, or close relatives were affected. He knows that he is the bearer of the hereditary type of disease. His chance of passing on the gene is one-half, and the

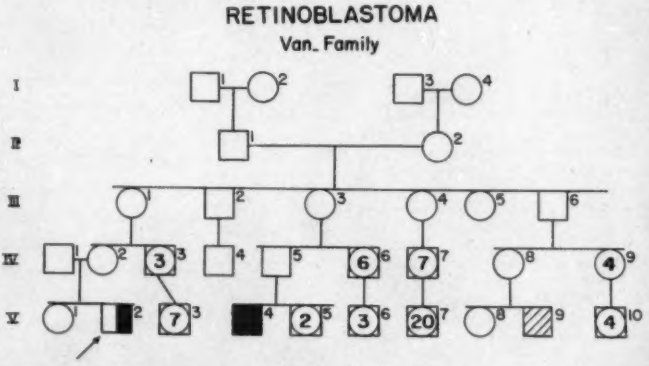


Fig. 10.—The proband, *V 2*, had a second cousin *V 4* with pathologically diagnosed bilateral disease. Another second cousin was reported as retinoblastoma, but when the family was finally traced and the pathological diagnosis obtained, it was glioma of the pons. The maternal side of *V 4* was not traced, but the paternal side of *V 2* was traced. Those traced were 4 great-grandparents, 2 grandparents, 13 great aunts and uncles, (with two more and their descendants not traced), 47 children and 54 grandchildren of the great aunts and uncles, and 2 sibs of the father *IV 1*, and their 2 children. All were normal. The relatives of the husband of *III 1* were traced and were normal. They were his 2 parents, his 3 sibs, their 19 children, and 32 grandchildren. These are not shown in the figure.

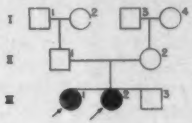


Figure 11

Fig. 11.—The father in this family was adopted as a small child; no family history was known. On the maternal side, four great-grandparents, two grandparents, nine great aunts and uncles were traced, and all were normal. The 12 children of the great aunts and uncles could not be traced, but were reported as normal. The mother had no sibs.

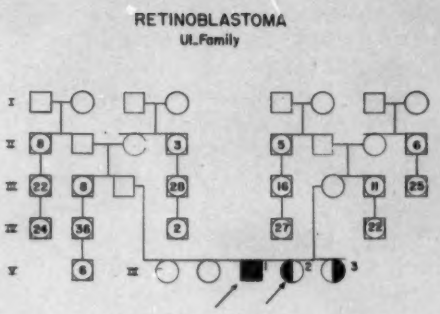


Figure 12

Fig. 12.—The complete family history is represented in the pedigree. *V 3* was born in Feb., 1959, two years after the interview with the family; her right eye became affected before the age of three months.

risk that any one of his offspring will be affected will be one-half times the degree of penetrance which the gene will show in the offspring. This is an unknown quantity. He should not have children. The second class of persons is made up of the parents who have produced one child with the disease, although they are normal, and there is no known case in the family apart from their affected child. They are faced with the problem of knowing that future children may be affected, yet they may be told quite truthfully that many parents in this situation have continued their family and there have been no further victims of the disease. On the other hand, similar families have continued to reproduce and what was at first an isolated case in now one of several affected sibs. Such families are shown in Figures 4, 11, 12, 13, 14. In order to deduce what has happened to other families in this situation, one must determine how often such families had children after the first affected one, and how many families had unfortunate results. In this series 145 sibships were found. In 55, no children were born after the first affected child, so they contribute nothing to the answer. In the 90 families in which subsequent pregnancies did occur, 6 or 6.67% had one or more affected children. The number of affected born *after the first affected* ranged from one to five.

The third class of persons are those who might inquire concerning their risk of bearing affected children when they are isolated instances of the disease who have grown to maturity. It might be a phenocopy in them, in which case their children should be normal. It might be a somatic mutation in them, because the majority of cases who survive are unilateral. Seventy per cent of survivors in this series were unilateral cases. Again, their children should be nor-

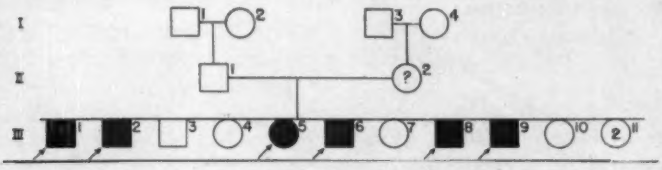


Fig. 13.—Six children all with bilateral disease were born to two parents, both supposedly without retinoblastoma. The mother had one microphthalmic eye, never removed, which she refused to have examined. The family was traced as far as possible. On the paternal side, 4 great-grandparents, 2 grandparents, 12 great aunts and uncles, 17 of their children (another was not located), 26 of their grandchildren (nothing known of 9 others) and 26 of their great grandchildren, 4 sibs of the father (one of them died early infancy), and 6 of the sibs' children were traced. All traced were normal, and the family reported no eye cancer in those not located. On the maternal side, 4 great-grandparents, 2 grandparents, 8 great aunts and uncles (with 4 of them not located), 12 of their children (8 not located) and 6 of their grandchildren, the mother, her 9 sibs and their 21 children have been traced. All six children were located separately through different sources. Three died in childhood, and three are living; the oldest is 28 with no children at the last report.

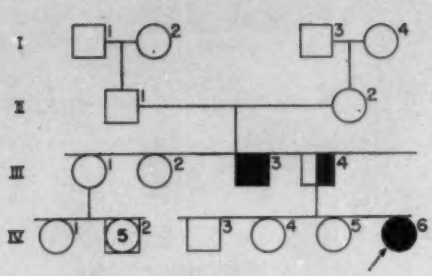


Figure 14

Fig. 14.—Here a unilaterally affected parent had a brother, with both eyes affected, who died in childhood. His fourth child is a bilateral case also. The father has remained unilateral through the 43 years since the enucleation. The paternal side of the family was traced as follows: 2 great-grandparents (nothing known of other 2), 2 grandparents, 12 great aunts and uncles (3 living in Sweden, not traced), 16 children of great aunts and uncles (8 of these and their descendants not traced, but said not to be blind), 8 grandchildren of great aunts and uncles, a sister of the father who died in early infancy, and a sister who had 6 children, one dying in early infancy. On the maternal side, not shown in the figure there were 4 great-grandparents, 2 grandparents, 5 great aunts and uncles, their 8 children, the mother, her 5 sibs and their 14 children were traced, and all were normal.

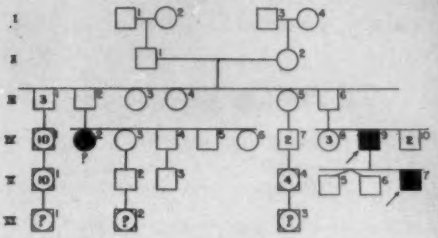


Figure 15

Fig. 15.—The father and child were both probands. His first cousin was said by her sibs to have died following removal of the eyes for cancer at the age of two. No record of the operation can be found, the doctor having died many years ago. The family of the wife of *III 6*, not shown in the pedigree, was traced, and her two parents, her 8 sibs, their 24 children, and 62 grandchildren, and 25 great-grandchildren were all normal. The maternal side of *V 7*'s family was traced with 4 great-grandparents, 2 grandparents, 11 great aunts and uncles, their 24 children, 47 grandchildren, 14 great-grandchildren, the mother of *V 7*, her 8 sibs, their 23 children and 14 grandchildren all being normal.

mal. They might be examples of the hereditary type who have remained unilateral. There are very few cases reported in the literature, however, where isolated cases have married and produced children. There were two in this series; each has had one child, and neither has been affected, although they are still under three. Tucker and his co-workers[4] have reviewed the literature and added eight cases of their own. Their tentative conclusion based on these few cases is that about 25% of sporadic cases will produce affected children, and that 40% to 50% of their children are likely to be affected. As these authors point out, more data are needed on this question.

Summary

Retinoblastoma based on a study of the cases in Ohio over a period of 17 years shows that intensive investigation into the family history reveals collateral lines affected in 10.5% of what have been regarded as sporadic cases. The mode of inheritance agrees with the interpretation that the gene is dominant, but in these families the average penetrance is much lower than that found by other workers. The mutation rate is in between that found by Neel and Falls[3] in Michigan on the one hand, and by Vogel[5] in Germany on the other. It was 1.76×10^{-5}. The frequency of the condition was found to be once in every 23,287 children who had survived as long as one year. The question of risk for future children being affected is discussed for the following three groups of persons who know that a risk exists: (1) those who are hereditary cases, surviving to maturity; (2) normal parents with no history of it in their families who have produced one affected child, and (3) sporadic cases who have grown to maturity.

This work was sponsored by a grant from the Department of Health, Education and Welfare from June, 1956 through May, 1959. My thanks are due to this agency. I also thank the many physicians, hospitals, the Director of the Columbus State School for the Blind, and the Director of the Ohio Services for the Blind, for their cooperation in furnishing names of retinoblastoma cases.

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REFERENCES

1. Franceschetti, A., and Bischler, V.: Rétinoblastome et hérédité, Arch. Julius Klaus- Stiftg. Vererbungsforschg 21:332, 1946.

2. Falls, H. F., and Neel, J. V.: Genetics of Retinoblastoma, A.M.A. Arch. Ophth. 46:367-389 (Oct.) 1951.

3. Neel, J. V., and Falls, H. F.: The Rate of Mutation of the Gene Responsible for Retinoblastoma in Man, Science 114:419-422, Oct. 19, 1951.

4. Tucker, D. P.; Steinberg, A. G., and Cogan, D. G.: Frequency of Genetic Transmission of Sporadic Retinoblastoma, A.M.A. Arch. Ophth. 57:532-535 (April) 1957.

5. Vogel, F.: Über Genetik und Mutationsrate des Retinoblastoms (Glioma retinae), nebst einigen allgemeinen Bemerkungen über die Methoden zur Mutationsratenschätzung beim Menschen, Ztschr. menschl. Vererb. u. Konstitutionslehre 32:308-336, 1954.

Angioid Streaks and Sickle Cell Anemia

A Report of Two Cases

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In recent years, the large majority of angioid streak cases has been correlated with either pseudoxanthoma elasticum or osteitis deformans (Paget's disease). It is becoming more unusual to find reports of angioid streaks unrelated to one of these diseases. This is chiefly due to more astute clinical recognition of pseudoxanthoma elasticum, and probably because diagnosis of the streaks has become more precise. This paper presents two young men with angioid streaks, neither of whom had the commonly associated systemic diseases; both had sickle cell anemia. These two patients have been referred to in an earlier publication.[1] Angioid streaks in cases of sickle cell disease have not been previously reported.

Report of Cases

CASE 1.—A 30-year-old Negro man was twice admitted to the National Institute of Neurological Diseases and Blindness for diagnostic studies pertaining to ocular lesions identified as angioid streaks. He was first admitted in April, 1958, and later in December, 1958, for extensive evaluations.

The patient gave a history of multiple complications of sickle cell anemia since the age of 10, having had periodic bouts of joint pain and several blood transfusions yearly. Until recent years he had chronic leg ulcers which required persistent medical treatment. He had never had eye complaints. His family history was incomplete, but there was no known eye or blood disease; his mother and three siblings, who were examined ophthalmoscopically, had no relevant ocular abnormalities.

During both admissions, pertinent physical findings were as follows: The patient was a tall (6 ft. 3 in.), languid, dark-skinned Negro man who intermittently complained of general malaise and pain in the extremities. The skin was carefully examined by a dermatologist familiar with pseudoxanthoma elasticum; it showed no evidence of this disease. There was a small keloid on the anterior chest and extensive scarring and atrophy of the skin above the ankles where chronic leg ulcers had formerly existed. The mucous membranes and nail beds were pale. The heart was enlarged on percussion and there was a low-pitched systolic murmur at the apex. The peripheral pulses were readily palpable. The liver and spleen were not detectably enlarged, but the abdomen was protuberant and difficult to examine.

Eyes: Vision was 20/20+3 in the right eye and 20/20+1 in the left, and near vision was Jaeger 1. The sclerae were moderately icteric. Biomicroscopy of the bulbar conjunctivae showed isolated, varicose, capillary dilatations containing clumped blood cells. With prolonged observation, the circulation in these segments would renew and other isolated segments form. The remainder of biomicroscopy was unremarkable. The visual fields showed minimal bilateral blind spot enlargement, but were otherwise full. Intraocular tension was normal in both eyes. Funduscopic examination: In both eyes the media were clear; the discs were normal in appearance. Bi-

Submitted for publication June 12, 1959.

From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U.S. Department of Health, Education and Welfare.

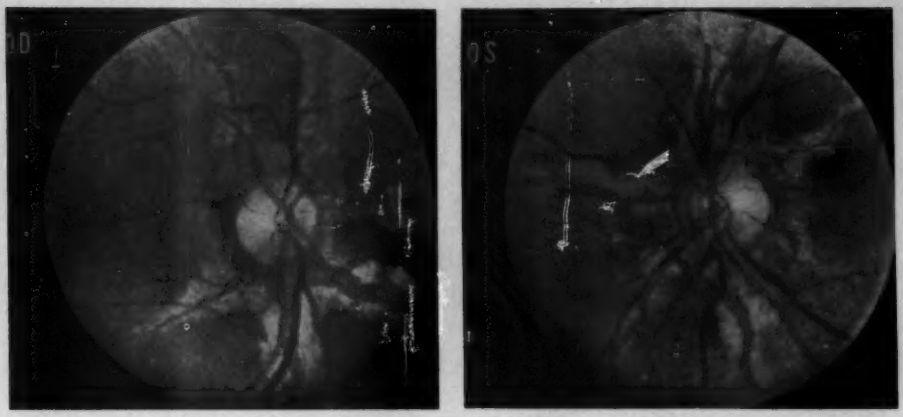
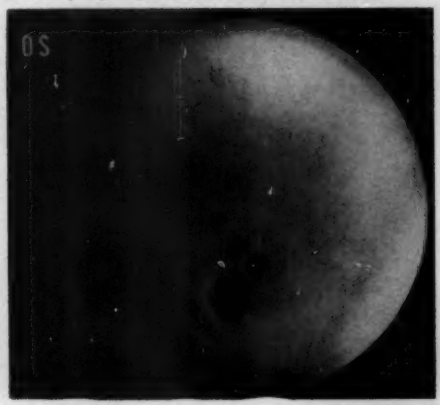


Fig. 1 (Case 1).—Fundus photographs showing angioid streaks.

laterally, just peripheral to the disc margins, there was an irregular plexus of brownish-black angioid streaks from which five major radial streaks extended beyond a whitish, peripapillary, star-shaped bed and tapered to the midperiphery of the fundus where they terminated (Fig. 1). Near the discs the streaks were one-third to four times the diameter of the retinal arteries. The retinal vessels, superficial to the streaks, showed no abnormality of A/V ratio nor increase in tortuosity; except in the fundus periphery, the vessels were normal. Throughout the fundi there was a peppery granularity of pigmentation. Occasional, small chorioretinitic spots were scattered in the mid and far portions of the fundi, seemingly unrelated to the angioid streaks. There were no hemorrhages, exudates, or cytoid bodies. "Sheathing" of the fine vessels was noted in the far and mid-periphery; frequently this seemed to consist of a whitish quality of the underlying fundus; but elsewhere fine peripheral vessels were white-coated. Scattered areas of greyness were just discerned in the furthermost visible fundus. The maculae appeared normal. In the inferotemporal periphery of the left eye there were two, small salmon-colored spots; these appeared as round, luminous, pink spots seen through fenestrations in a sheath of connective tissue proliferation (Fig. 2). They had not been noted prior to December, 1958.

Laboratory examinations included the following: sickle cell preparation, immediately positive; hemoglobin electrophoresis: S hemoglobin only; hematocrit 23%, WBC 8,400, platelets 565,000, reticulocytes 12.3% to 20%, coagulation time: 45 minutes (silicone); bilirubin 3.4 mg. %, serum uric acid 9.8 mg. %, BUN 7 mg. %, alkaline phosphatase 2.8 B-L units, calcium 10 mg. %, phosphorus 4.4 mg. %, and a nonreactive VDRL microflocculation test. X-rays of the skull, chest, hands, ankles, feet, legs, and knees revealed the following:

Fig. 2 (Case 1).—Photograph of "salmon spots" in far periphery of left fundus.



There was prominence of the trabecular pattern of the bones in the extremities which was compatible with sickle cell anemia, but no evidence of vascular calcification nor of other bony abnormalities. Oscillometric studies of the extremities were all within normal limits. Skin biopsies of the cervical and axillary skin showed no evidence of pseudoxanthoma elasticum.

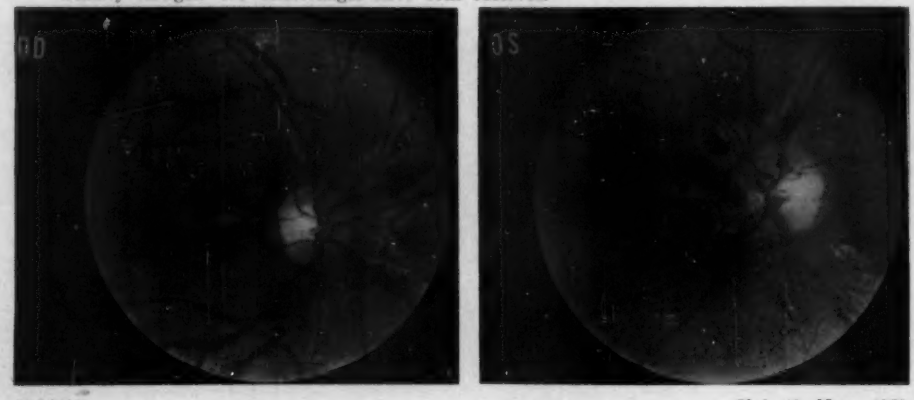
CASE 2.—A 23-year-old Negro man was also referred for appraisal of ocular lesions of unknown character. At the time of his first examination in July, 1957, these lesions were identified as angioid streaks. The patient was subsequently admitted to the National Institute of Neurological Diseases and Blindness in April, 1958, and again in December, 1958.

Since early childhood, the patient had a history of severe manifestations of sickle cell anemia which had required multiple blood transfusions prior to the age of 12. In general, two or three times a year he had had repeated episodes of arthralgia, fever, malaise, and icterus. In 1954, he had a cholecystectomy for cholelithiasis. During the previous several years, leg ulcers had required persistent treatment. There was no relevant history of eye complaints, although the patient had experienced certain hysterical visual phenomena. Family history was sparse. His parents were dead and apparently had no known systemic disease. Of three half siblings (same mother), none was known to have sickle cell disease. Two of them were examined ophthalmoscopically in August, 1957, without positive results.

Pertinent physical findings have been as follows: The patient was a tall (6 ft. 3 in.), slender, dark-skinned, Negro with marked speech impairment from stuttering. Careful examination of the skin showed no evidence of pseudoxanthoma elasticum. There were small leg ulcers above the medial maleoli which were surrounded by extensive scarring and areas of depigmentation, demonstrative of former, more widespread ulceration. The heart was enlarged to percussion, and there was an apical systolic murmur. All peripheral pulses were readily palpable. There was a diagonal right upper quadrant, well-healed abdominal incision. The liver edge was percussed one to two finger breadths below the right costal margin. The spleen was not palpable. The remainder of the general physical examination was unremarkable.

Eyes: Vision was 20/20+3 bilaterally and near vision Jaeger 1+. There was minimal icterus at each examination. On biomicroscopy, linear capillary vessel fragments were noted quite diffusely over the bulbar and fornix conjunctivae. There were isolated, varicose, aneurysmal dilatations whose afferent and efferent connections were not visible. These changes were com-

Fig. 3 (Case 2).—Fundus photographs showing angioid streaks. The dark areas are pigmentary changes. No hemorrhages have been observed.



parable to the findings in Case 1. The patient's visual fields were normal in 1957, and early 1958, but subsequently were limited to approximately 10 degrees from the point of fixation in all meridians. In view of the same field limitations with all test objects at one and two meters, the field abnormalities were considered hysterical and in keeping with past and present personality disorder which had necessitated psychiatric consultation. On funduscopic examination, the media of both eyes were clear. The discs and maculae were normal. About one quarter disc diameter from the disc margins, radial angioid streaks extended from their annular interlacing (Fig. 3). These were branched, brownish-black, irregular striae lying deep to the retinal vessels which extended a distance of one to three disc diameters from the disc margins. Particularly proximally the streaks characteristically lay in a white bed. The retinal vessels had normal A/V ratio, and except for the small peripheral vessels there was no increase in tortuosity. There were no hemorrhages or exudates throughout the period of observation. Diffusely, both fundi had a mottled pigment dispersion. Near the ora serrata, small, indistinctly seen grey patches were noted which could not be precisely defined. There was a marked distinctness to the precapillary vasculature at many sites in the fundi. In the far periphery fine retinal vessels showed increased tortuosity; a number of these seemed to lie in a faint white bed. Again, as in the previous case, true vascular sheathing was minimal.

Laboratory studies during the two admissions included: Sickle cell preparation, immediately positive. Hemoglobin electrophoresis obtained by paper, starch block, and moving boundary techniques showed the presence of S hemoglobin only. In addition, the hemoglobin was 8.8 gms., hematocrit 27%, sedimentation rate 12 mm.; platelets 275,000; WBC 10,200, reticulocytes 10% to 19%, BUN 9 mg. %, serum uric acid 9.5 mg. %, bilirubin 3.4 mg. %, alkaline phosphatase 2.7 B-L units, calcium 9.9 mg. %, and phosphorus 4.2 mg. %. The coagulation time was 30 minutes (silicone), and the VDRL microflocculation test nonreactive. The electroencephalogram record was within normal limits. Bone changes of sickle cell anemia were found in x-rays of the skull, chest, and extremities where minimal periosteal changes were indicated by irregular, cortical bone formation, most evident in the left femur. One medullary area of sclerosis in the distal, right radius was compatible with an old infarction. There was no x-ray evidence of intravascular calcification. Oscillometric studies of the extremities were normal. A skin biopsy taken at the right axilla was obtained in an effort to rule out occult pseudoxanthoma elasticum. Microscopic examination showed normal tissue.

In both cases reported above, fundus photographs and repeated examinations have failed to show any change in the appearance of the angioid streaks during the interval that the patients have been followed.*

Comment

There has been a long controversy over the pathogenesis of angioid streaks. Much of it has historical interest only, for many theories were unsubstantiated. Some authors postulated the primary role of hemorrhage and vascular insufficiency in the retina or choroid; others thought that retinal or choroidal folds were responsible for the streaks. A third group has contended that pigmentation related to normal or aberrant choroidal vessels is responsible for the clinical picture. These concepts have been extensively reviewed [2,3] and will not be restated, in that each lacks convincing evidence.

* Since the preparation of this paper, at the alumni meeting of the Eye Institute of Columbia University, Dr. DuPont Guerry has commented upon four cases of angioid streaks in patients with sickle cell disease. These patients are currently under study. A third case has come to my attention since submitting this paper. The angioid streaks are again classical; there are no other associated diseases, and hemoglobin electrophoresis shows S hemoglobin only.

One of the earlier concepts was that the streaks represent clinically visible breaks in Bruch's membrane.[4] Pathological studies have subsequently supported this view † and have shown, in addition to breaks, basophilia of the membrane. Since basophilia and even breaks in Bruch's membrane have also been found in certain normal and pathological eyes without clinical evidence of angioid streaks,[9,10] there remain differences of opinion of the manner in which the breaks become clinically visible.[7,8]

Angioid streaks are uncommon. As pointed out in the introduction, the great majority of cases is associated with either pseudoxanthoma elasticum or Paget's disease. There is no reason to believe that these generalized diseases are fundamentally related. The literature contains only three authenticated cases in which pseudoxanthoma elasticum and Paget's disease have been known to coexist.[11,12,13] A fourth case has just been recognized,[14] again in association with angioid streaks. Paget's disease was far advanced, but the signs of pseudoxanthoma elasticum were so minimal that only after biopsy diagnosis had been made were suggestive skin changes identified. In both entities, vascular disease is a frequent observation—in particular, a common ground is medial calcification of the larger arteries [15,16,17,18] where there is plentiful elastic tissue. It is quite probably this calcification at certain elastic tissue sites rather than vascular disease *per se* which causes basophilia of Bruch's membrane, breaks in the membrane, and hence, angioid streaks. This view has been previously suggested.[9,7] However, in five of the six pathological studies referred to above, pseudoxanthoma elasticum was present. Angioid streak eyes of Paget's disease have not yet been examined histologically, but basophilia and breaks in Bruch's membrane were found in one of three eyes obtained from Paget's disease patients.[9] Funduscopic examination was not recorded in that case.

The remainder of angioid streak cases is a small, miscellaneous group. Some of these cases have been related to senile elastosis, local eye diseases, various vascular diseases with retinal hemorrhages, or reported as incidental findings. Many such cases are in the older literature and diagnostic criteria were then less uniform. Sufficiently extensive physical examinations and laboratory procedures have often not been done to rule out pseudoxanthoma elasticum. In one series of angioid streaks, for example, two patients were found to have positive skin biopsies in whom the skin appeared clinically normal.[19] There is less error in overlooking occult Paget's disease; for although it has been found in three per cent of autopsies on patients over age thirty-nine,[20] angioid streaks are seemingly a late manifestation, at which time the clinical diagnosis is evident.

The two patients reported in this paper belong in the small, miscellaneous group of angioid streak cases. Pseudoxanthoma elasticum and Paget's disease have been virtually ruled out by the negativity of skin biopsies, skeletal and soft tissue x-rays, alkaline phosphatase determinations, and physical examinations. The only systemic disease is sickle cell anemia.

Ocular manifestations of this anemia have not as yet been thoroughly characterized. The classification of abnormal hemoglobins by electrophoresis is a relatively new method, and it is only since this has been available that separation of the various clinical entities of sickle cell disease has become possible. Sickle cell anemia, homozygous hemoglobin S, has been thought to show less marked ocular changes that the severe retinopathies of heterozygous states such as sickle cell hemoglobin C disease.[1,21,22] Previously only dilatation and tortuosity of the retinal veins,[21] then pigmentary and proliferative changes [22] were reported in electrophoretic-

† References 5, 6, 7, 8. More recently, comparable pathological changes have been found in angioid streak eyes by Dr. F. P. Calhoun, Jr. who reported one case in March, 1959, at the Ophthalmic Pathology Club, and by the author in a similar eye obtained from the Wilmer pathology laboratory through the kindness of Dr. James Duke.

ally proven sickle cell anemia. More recently, sheathing and obliteration of the peripheral fundus vessels, retinal hemorrhages, and segmental dilatations of the conjunctival vessels have been observed in the anemia ‡ as well as in heterozygous sickle cell abnormalities. Except for retinal hemorrhages, and dilatation and tortuosity of the larger retinal veins, these signs were also present in the two cases reported above. "Salmon-colored spots," seemingly peculiar to hemoglobinopathies,[1] have not been formerly described in the anemia and were present in Case 1. A possible explanation of the usually less advanced fundus changes in homozygous patients might be related to the shorter life span of sickle cell anemia.

Sickle cell anemia has three known aspects which could theoretically relate to the occurrence of angioid streaks in these two patients: anemia, retinal hemorrhages, and occlusive vascular disease. Some evidence exists that anemia might play a role in the pathogenesis of angioid streaks, although anemia is not a component of either pseudoxanthoma elasticum or Paget's disease. There is a case report of angioid streaks occurring within ten years of an almost exsanguinating hemorrhage from idiopathic thrombocytopenia;[23] this same author refers to another possible example: a fundus drawing indicating typical angioid streaks which was made postmortem, following death from exsanguination.[24] These cases suggest that angioid streaks might follow severe acute episodes of anemia such as the hemolytic crises of homozygous sickle cell patients. On the other hand, no basic relationship between angioid streaks and retinal hemorrhage has been shown. Some authors have described progression of the streaks in the wake of retinal hemorrhages, but in many cases (as in those described above) angioid streaks have been present for years without evidence of ocular hemorrhage. Finally, unlike pseudoxanthoma elasticum and Paget's disease, the vascular changes of sickle cell anemia do not include medial calcification, but are chiefly thrombo-occlusive in nature. A theory that angioid streaks result primarily from vascular impairment of the choriocapillaris with resultant damage to Burch's membrane[25] has not been substantiated. None of the four published pathological studies showing breaks in Bruch's membrane[5,6,7,8] had sufficiently marked vascular changes in the retina or choroid to have pathogenic significance.[8] Nevertheless, in sickle cell anemia where there is thrombotic disease of the small vessels, an impairment of the choriocapillaris circulation deserves consideration.

Angioid streaks have been infrequently described in Negroes. There was pseudoxanthoma elasticum in two of six Negro cases identified in one review;[9] in the original reports of the others, there is inadequate information to suspect sickle cell disease, and nothing to suggest the anemia. One case related to pseudoxanthoma elasticum has been examined histologically,[8] and two other cases, one with pseudoxanthoma elasticum, are currently under study.[26]

Summary

Angioid streaks in two patients with sickle cell anemia have been reported.

The relationship between angioid streaks and the two most commonly associated diseases has been considered with particular regard to the pathogenesis of the streaks. A common denominator with sickle cell anemia has not been established, but certain possibilities have been discussed.

Ophthalmology Branch, National Institutes of Health (14).

REFERENCES

1. Goodman, G.; von Sallmann, L., and Holland, M. G.: Ocular Manifestations of Sickle-Cell Disease, A.M.A. Arch. Ophth. 58:655-682, 1957.

2. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, The C. V. Mosby Company, 1941, Vol. 3, pp. 2413-2418.

3. Cowper, A. R.: Angioid Streaks. Tears in Bruch's Membrane or Pigmented Choroidal Vessels (?), A.M.A. Arch. Ophth. 51:762-782, 1954.

4. Kofler, A.: Beiträge zur Kenntnis der Angioid Streaks, Arch. Augenh. 82:134-149, 1917.

‡ From observations made on patients examined at the National Institutes of Health.

5. Hagedoorn, A.: Angioid Streaks, von Graefes Arch. Ophth. 21:746-774, 935-965, 1939.

6. Böck, J.: Zur Klinik und Anatomie der gefässähnlichen Streifen im Augenhintergrund, Ztschr. Augenh. 95:1-50, 1938.

7. Klien, B. A.: Angioid Streaks, Am. J. Ophth. 30:955-968, 1947.

8. Verhoeff, F. H.: Histological Findings in a Case of Angioid Streaks, Brit. J. Ophth. 32:531-544, 1948.

9. Scholz, R. O.: Angioid Streaks, von Graefes Arch. Ophth. 26:677-695, 1941.

10. Verhoeff, F. H., and Sisson, R. J.: Basophilic Staining of Bruch's Membrane, von Graefes Arch. Ophth. 55:125-127, 1926.

11. Woodcock, C. W.: Pseudoxanthoma Elasticum, Angioid Streaks of Retina and Osteitis Deformans, Tr. Cleveland Dermat. Soc., A.M.A. Arch. Dermat. & Syph. 65:623, 1952.

12. Shaffer, B.; Copelan, H. W., and Beerman, H.: Pseudoxanthoma Elasticum, A.M.A. Arch. Dermat. 76:622-633, 1957.

13. Larmande, A., and Margaillan, A.: Maladie de Paget et syndrome de Groenblad-Strandberg, Bull. et Mém. Soc. fran. d'opht. 70:206-215, 1957.

14. Paton, D.: Unpublished data.

15. Carlborg, U.: Studies of Circulatory Disturbances, Pulse Wave Velocity and Pressure Pulses in Larger Arteries in Cases of Pseudoxanthoma Elasticum and Angioid Streaks; Contribution to Knowledge of Function of Elastic Tissue and Smooth Muscle in Larger Arteries, Acta med. scandinav. Supp. 151, pp. 1-209, 1944.

16. Scheie, H. G., and Hogan, T. F.: Angioid Streaks and Generalized Arterial Disease, A.M.A. Arch. Ophth. 57:855-868, 1957.

17. McKusick, V.: Heritable Disorders of Connective Tissue. Paget's Disease of Bone, J. Chron. Dis. 3:537-542, 1956.

18. Sornberger, C. F., and Smedal, M. I.: The Mechanism and Incidence of Cardiovascular Changes in Paget's Disease (Osteitis Deformans). A Critical Review of the Literature with Case Studies. Circulation, 6:711-726, 1952.

19. Van Embden Andres, G. H.: Afwijkingen aan de inwendige organen bij Pseudoxanthoma Elasticum en Angioide Strepen, Monograph, Groningen, May, 1952.

20. Schmorl, G.: Anatomische Befunde bei einem Fall von Osteopoikilie, Fortschr. Geb. Röntgenstrahlen 44:1-8, 1931.

21. Hannon, J. F.: Vitreous Hemorrhages Associated with Sickle-Cell-Hemoglobin C Disease, Am. J. Ophth. 42:707-712, 1956.

22. Kennedy, J. J., and Cope, C. B.: Intraocular Lesions Associated with Sickle Cell Disease, A.M.A. Arch. Ophth. 58:163-168, 1957.

23. Yatzkan, D. N.: Angioid Streaks of the Fundus in Association with Posthemorrhagic Amaurosis Am. J. Ophth. 43:219-222, 1957.

24. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, Vol. 3, Plate XLVIII, Fig. 2156.

25. Bonnet, P.: Les stries angioïdes de la rétine, Arch. d'ophth. 50:721-750, 1933.

26. Scheie, H. G.: Personal communication to the author.

Diabetic Retinopathy and the Pituitary

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The influence that pituitary function has on diabetes has long been known. The existence of diabetic retinopathy in patients having pituitary tumors has been referred to only briefly in the literature. Hypophysectomy has been performed to try to control diabetic retinopathy; the rationale being to eliminate pituitary factors possessing diabetogenic action.

The causative factors producing diabetic retinopathy or accounting for its progression are not known. Other than the time required for the development of diabetic retinopathy, the only factor seemingly related to the incidence and severity of retinopathy has been the degree of control of the diabetes.[1] The pituitary gland in diabetes shows no constant significant structural change.[2]

Pituitary Factors Possessing Diabetogenic Action

A pure diabetogenic substance has not been isolated. It is generally agreed that the pituitary adrenocorticotrophic and growth hormones exert a diabetogenic action. Young[3] has speculated that the pituitary diabetogenic substance and the growth hormone might be identical. Others[4] felt that there may be a specific factor in the pituitary, not growth hormone or corticotropin (ACTH) which competes with insulin. De Bodo and Sinkoff[5] considered the growth hormone to have more of a diabetogenic effect than the adrenocortical steroids. They found that the adrenalectomized dog was much less sensitive to insulin than the adrenalectomized-hypophysectomized dog, and therefore, inferred the existence of an anterior pituitary factor other than corticotropin that exerted a significant effect on carbohydrate metabolism.

Diabetogenic Factors and Retinopathy

The evidence that adrenocorticotrophic hormone, cortisone, or its derivatives can produce diabetic retinopathy in humans is not convincing. Becker[6] did report the experimental production of an ophthalmoscopic picture resembling early diabetic retinopathy in rabbits made diabetic with alloxan and subsequently injected with corticotropin. He also knew of two patients who developed lesions resembling capillary aneurysms in their fundi after treatment with corticotropin. The lesions disappeared after cessation of the corticotropin therapy. He felt therefore that retinal lesions could be produced by corticotropin. However, Rosen[7] and Marble[8] were not successful in producing or demonstrating diabetic retinal lesions by injecting cortisone in diabetic rabbits. Clinically, considering the widespread usage of steroids at this time, it is surprising that diabetic retinopathy has not been reported much more often as a consequence of such therapy if the adrenocorticotrophic hormones were a significant contributing factor. Moreover, cortisone has been used with apparent benefit in the management of diabetic retinopathy.[9]

Experimentally, cortisone[10] and a protracted course of an anterior pituitary extract have produced Kimmelstiel-Wilson nodular lesions in the kidneys as well as diabetes in the dog.[11] Friedenwald expressed the opinion that the retinal aneurysms of diabetic retinopathy and the Kimmelstiel-Wilson glomerular nodules were joint manifestations of the same process; and that the hyaline of the Kimmelstiel-Wilson nodule resembles the thickened

Submitted for publication May 21, 1959.

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walls of retinal capillary aneurysms.[12] Kimmelstiel, on the other hand, recently reported that the retinal lesions were distinct entities.[13] Volk[14] also pointed out the differences between the retinal and renal lesions. There is no doubt that diabetic retinopathy can exist without intercapillary glomerulosclerosis, and that the retinopathy precedes the glomerulosclerosis and is not due to it.[15]

Poulsen[16] reported disappearance of retinopathy in a diabetic who developed Simmonds' disease following pregnancy. His case supports the reasoning that hypopituitarism may have a beneficial effect on diabetic retinopathy. There have been reports that diabetics at routine necropsies furnish an increased number of patients with pituitary necrosis.[17,18] These investigators made no observations or reference to the patient's retinal status. It is, however, uncommon for diabetic retinopathy to reverse itself permanently once it has appeared.

Diabetic Retinopathy with Pituitary Tumors

There appears to be only two studies in the literature referring to the occurrence of diabetic retinopathy in diabetic patients with either acromegaly or Cushing's syndrome. In 16 acromegalics, Ricketts[19] reported the retina did not reveal any abnormalities except in two of three cases in which diabetes was also present. No mention was made as to whether the diabetes had preceded the acromegaly. He also found no diabetic retinopathy in 10 patients with Cushing's syndrome in which 7 of these patients also had diabetes. McCullogh and Alivasatos[20] reported diabetic retinopathy in 3 of 21 acromegalic diabetics and in 2 out of 21 patients having Cushing's syndrome and diabetes.

Present Studies

In this study, diabetic retinopathy did not occur as a frequent complication in 66 patients having pituitary tumors. Diabetes mellitus occurring as a complication or appearing after the clinical onset of the pituitary tumor did not alter this infrequent incidence of retinopathy.

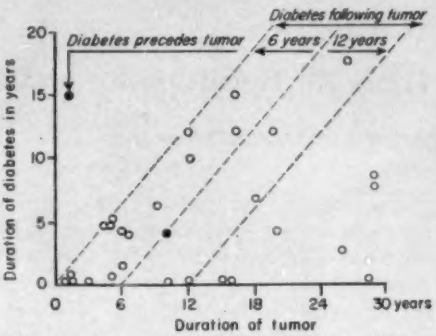

Fig. 1.—The period at which diabetes makes its appearance is variable with respect to the onset of the pituitary tumor.
○ patients without diabetic retinopathy.
• patients with retinopathy.

The 66 pituitary tumors * were clinically diagnosed as follows: eosinophil in 42, chromophobe in 14, basophil in 6, mixed type in 3, and unknown in one case. Pathological studies of the tumors were not performed, so that histological proof of the above diagnoses was not obtained, nor was any evaluation of pituitary function made. The majority of the patients (54%) were 21 to 40 years of age at the time of recognition of symptoms establishing the clinical onset of the tumor. Thirty per cent were 41 to 60 years of age. There were 38 female and 28 male patients.

Thirty patients of the 66 had coexisting diabetes. In 27, the diabetes was associated with the eosinophil tumors, in 2 with the basophil, and in one case with a chromophobe tumor. Twenty-one of the diabetics required insulin in their management and the remaining patients were newly discovered diabetics as determined by abnormal glucose tolerance tests, and had not required insulin at that time. The duration of the diabetes and the pituitary tumors are illustrated in Figure 1. Twenty cases had their diabetes six years or less; of these, nine patients were newly discovered diabetics.

* Cases obtained from St. Francis Hospital, Evanston, Ill.: St. Luke's Hospital, Chicago, Illinois: Illinois Research and Educational Hospitals.

Four patients had their diabetes 7 to 10 years, and 6 patients had diabetes of 12 to 17 years' duration. The time that diabetes may become manifest is quite variable with respect to the duration of the pituitary tumor. In one case the diabetes preceded the onset of the tumor by 14 years. In the remaining 29 patients, diabetes made its appearance within the first six years of the pituitary tumor (55%), and in 22 (75%) within the first twelve years (Fig. 1). The longer the duration of the pituitary tumor, the greater percentage of patients developing diabetes (Fig. 2).

Two patients had diabetic retinopathy in the entire group of 66 pituitary tumor patients, and of the 30 patients who had associated diabetes these two patients represented 6.7% (Table). If we exclude the lone case in which diabetes preceded the pituitary tumor by 14 years, the incidence of diabetic retinopathy would then be 1.5% for pituitary tumor patients, and 3.8% for those patients developing diabetes following a pituitary tumor because only one such patient had retinopathy. This patient had papilledema secondary to her eosinophilic adenoma of the pituitary for which she received two courses of x-ray therapy prior to being seen at the Illinois Research and Educational Hospitals. At the time she was seen, papilledema was still present and was later complicated by a hemorrhagic retinitis and subsequent bilateral retinal detachments. Organization of the associated vitreous hemorrhages resulted, followed by neovascularization and retinitis proliferans. Presumably, this retinopathy could have been the result of increased intracranial pressure, but it also resembles the findings of advanced diabetic retinopathy.

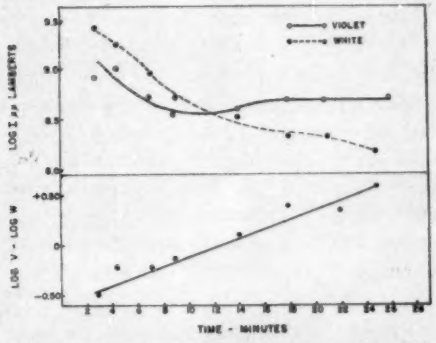

Fig. 2.—The longer the duration of the pituitary tumor, the greater the percentage of patients with diabetes.

This group of 30 patients with pituitary tumor and diabetes were then compared with a similar group of 30 diabetic patients without pituitary tumor, but matched identically for age, sex, and duration of diabetes (Table). There are strikingly fewer patients having diabetic retinopathy in the group with pituitary tumors and diabetes. Two patients out of 30 cases had diabetic retinopathy (6.7%) when diabetes and pituitary tumor coexisted, including the one case whose diabetes preceded the pituitary tumor by 14 years. This is compared (Table) to 8 patients developing diabetic retinopathy (26.6%) out of 30 cases having diabetes but no pituitary tumor.

Comments

It is unlikely that the pituitary directly contributes to the development of diabetic retinopathy because of the low incidence of retinopathy in patients with pituitary tumor and diabetes. Whether the diabetes that follows pituitary tumor is due to exaggerated physiologic amounts of growth hormone, corticotropin, a specific diabetogenic substance, a combination of these or some other as yet unidentified substance, these pituitary hormonal influences do not seem to be responsible for the retinopathy. The evidence in this series might be so construed as to argue that the pituitary may protect the individual against the development of retinopathy. This is unlikely.

There is no question of the pituitary's influence on the amount of insulin needed to control a diabetic, that is, increased insulin responsiveness occurs with decreased pituitary activity. However, severity of the diabetic state should not be gauged by the size of the dose of insulin required, but rather by the degree of "crippling" of the patient as a result of diabetic complications.

Pituitary Tumor and Retinopathy in Diabetics

	Without Retinopathy	With Retinopathy
Diabetes with pituitary tumor (30 cases)	28	2 (6.3%)
Diabetes and no pituitary tumor (30 cases)	22	8 (26.6%)

The above two groups of patients are matched identically for age, sex, and duration of diabetes. There are significantly fewer patients having diabetic retinopathy in those with pituitary tumor.

Diabetics with Kimmelstiel-Wilson's syndrome are severely damaged diabetics from the standpoint of their vascular involvement. Control of their urine and blood sugar levels is usually easily managed and often their insulin dosage is lowered or insulin not required for good diabetic control. Similar experiences with these patients are reported elsewhere.[21,22]

The increased insulin responsiveness that occurs in hypophysectomized diabetics resembles the insulin response one sees in labile diabetics in whom premature vascular degeneration develops and who are unusually sensitive to changes in insulin dosage. This is in striking contrast to steroid diabetes and that seen in acromegaly where insulin unresponsiveness is encountered and retinopathy is not common.

If a hormonal dysfunction causes retinopathy, there may be reason to suspect adrenal rather than pituitary factors. There is some evidence that diabetics without retinopathy have adrenal hypofunction, whereas those diabetics with retinopathy have excessive adrenocortical function.[23] The adrenals may be under prolonged stimulation from the stress resulting from frequent episodes of breaks in control, or periods of alternating hypoglycemia and hyperglycemia which are common to the labile diabetic.

The results of hypophysectomy[24,25] and adrenalectomy[26] in diabetes mellitus have been variable and not so therapeutically impressive as to warrant such a radical approach to the treatment of diabetic retinopathy. It is conceded that no other means to arrest retinopathy is known, and that knowledge obtained by these procedures may eventually lead to a definitive understanding of the mechanisms involved.

Kinsell[27] has suggested that a major factor in the vascular degeneration of diabetics may be the continuous disturbance of intracellular and extracellular osmotic relationships resulting from extreme fluctuations in blood sugar over months and years. These continuous physical and chemical alterations may be related to the proliferative and degenerative vascular changes in the eye, kidney, heart, central nervous system, or in the peripheral blood vessels. Relapses and spontaneous remissions in the progression of the vascular disease at irregular time intervals could then be explained according to fluctuating blood sugar concentrations. Continuing with this speculation, one might propose that these osmotic changes contribute to or may be causally related to other metabolic defects, such as, for example, the lipid changes[28,29] which are associated in patients having vascular degenerative disease. It seems reasonable to assume that no one etiological factor explains the pathophysiological disturbances that exist in the diabetic having vascular lesions.

Summary

The incidence of diabetic retinopathy in pituitary tumor patients is 3.0% in this series.

The incidence of diabetic retinopathy in diabetic patients with pituitary tumor is 6.7% and in a similar group of diabetic patients without pituitary tumor is 26.6%.

The time of appearance of diabetes during the course of pituitary tumor is variable. The majority of patients develop diabetes within the first six years after onset of the pituitary tumor.

The longer the duration of the pituitary tumor, the greater is the incidence of diabetes.

Pituitary tumors do not seem to contribute to the development of diabetic retinopathy. Whatever the pituitary hormonal

influence might be in promoting the development of diabetes, these same diabetogenic factors do not seemingly contribute to the production of diabetic retinopathy.

This rarity of diabetic retinopathy in pituitary tumor patients who develop diabetes mellitus should be considered before pituitary ablation is considered for the removal of diabetogenic factors of the pituitary in a patient with diabetic retinopathy.

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REFERENCES

1. Hardin, R. C.; Jackson, R. L.; Johnston, T. L., and Kelly, H. G.: The Development of Diabetic Retinopathy; Effects of Duration and Control of Diabetes, Diabetes 5:397-405 (Sept.-Oct.) 1956.

2. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, Ed. 9, Philadelphia, Lea & Febiger, 1952, p. 178.

3. Young, F. G.: The Relationship of the Anterior Pituitary Gland to Diabetes Mellitus, Acta medica scandinav. 135:275-288, 1949.

4. Stadie, Wm. C., Haugaard, N.; Marsh, J. B., and Hills, A. G.: The Chemical Combination of Insulin with Muscle and Its Hormonal Regulation, Tr. A. Am. Physicians 63:196-200, 1950.

5. de Bodo, R. C., and Sinkoff, M. W.: Role of the Growth Hormone in Carbohydrate Metabolism, Ann. New York Acad. Sci. 57:23-60, June 30, 1953.

6. Becker, B.: Diabetic Retinopathy, Ann. Int. Med. 37:273-289 (Aug.) 1952.

7. Rosen, D. A.; Becker, B.; Maengwyn-Davies, G. D., and Friedenwald, J. S.: The Influence of Heparin on the Cortisone Nephropathy of the Rabbit, Bull. Johns Hopkins Hosp.: 95:144-146 (Sept.) 1954.

8. Marble, A., in discussion on Adrenalectomy in Human Diabetes, Diabetes 3:374 (Sept.-Oct) 1954.

9. Coggeshall, C.: Personal communication to the author.

10. Bloodworth, J. M. B. Jr., and Hamwi, G. J.: Experimental Diabetic Glomerulosclerosis, Diabetes 5:37-43 (Jan.-Feb.) 1956.

11. Lukens, F. D. W., and Dohan, F. C.: Experimental Pituitary Diabetes of Five Years' Duration with Glomerulosclerosis, Arch. Path. 41:19-24 (Jan.) 1946.

12. Friedenwald, J. S.: Diabetic Retinopathy, J.A.M.A. 150:967-971, Nov. 8, 1952.

13. Kimmelstiel, P.: Glomerulosclerosis, J. Mt. Sinai Hosp. New York 23:657-662 (Sept.-Oct.) 1956.

14. Volk, D.: Dissimilarity of Retinal Microaneurysm and Glomerular Nodule in Diabetes, A.M.A. Arch. Ophth. 56:188-193 (Aug.) 1956.

15. Ashton, N.: Experimental Aspects of Diabetic Microangiopathy, Trans. Opth. Soc. U. Kingdom 77:127-140, 1957.

16. Poulsen, J. E.: The Houssay Phenomenon in Man; Recovery from Retinopathy in a Case of Diabetes with Simmonds' Disease, Diabetes 2:7-12 (Jan.-Feb.) 1953.

17. Brennan, C. F.; Malone, R. G. S., and Weaver, J. A.: Pituitary Necrosis in Diabetes Mellitus, Lancet 2:12-16, July 7, 1956.

18. Plaut, A.: Pituitary Necrosis in Routine Necropsies, Am. J. Path. 28:883-893 (Sept.-Oct.) 1952.

19. Ricketts, H. T.: The Problem of Vascular Disease in Diabetes, Proc. Am. Diabetes A. 8:153-163, 1948.

20. McCullogh, E. P., and Alivasatos, J. G.: Diabetes of Anterior Pituitary and Adrenal Cortical Origin, Diabetes 3:349-357 (Sept.-Oct.) 1954.

21. Zubrod, C. G.; Eversole, S. L., and Dana, G. W.: Amelioration of Diabetes and Striking Rarity of Acidosis in Patients with Kimmelstiel-Wilson Lesions, New England J. Med. 245:518-525, Oct. 4, 1951.

22. Runyan, J. W. Jr.; Hurwitz, D., and Robbins, S. L.: Effect of Kimmelstiel-Wilson Syndrome on Insulin Requirements in Diabetes, New England J. Med. 252:388-391, March 10, 1955.

23. Becker, B.; Maengwyn-Davies, G. D.; Rosen, D.; Friedenwald, J. S., and Winter, F. C.: The Adrenal Cortex and B-Vitamins in Diabetic Retinopathy, Diabetes 3:175-187 (May-June) 1954.

24. Luft, R.; Olivecrona, H., and Ikkos, D.: Hypophysectomy in Man; Further Experiences in Severe Diabetes Mellitus, Brit. M.J. 2:752-756, Sept. 24, 1955.

25. Schimek, R.: Hypophysectomy for Diabetic Retinopathy; Preliminary Report, A.M.A. Arch. Ophth. 56:416-425 (Sept.) 1956.

26. Wolff, H. J.; Kennedy, B. J., and Johnson, M. B.: Effect of Bilateral Adrenalectomy on Diabetes Mellitus, Minnesota Med. 40:318-321 (May) 1957.

27. Kinsell, L. W.; Lawrence, L.; Balch, H. E., and Weyand, L. D.: Hypophysectomy in Human Diabetes; Metabolic and Clinical Observations in Diabetics with Malignant Vascular Disease, Diabetes 3:358-366 (Sept.-Oct.) 1954.

28. Gofman, J. W.; Lindgren, F.; Elliott, H.; Mantz, W.; Hewitt, J.; Strisower, B., and Herring, V.: The Role of Lipids and Lipoproteins in Atherosclerosis, Science 111:166-171, 186, Feb. 17, 1950.

29. Engelberg, H.; Gofman, J. W., and Jones, H. B.: Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis, Metabolism 1:300-306 (July) 1952.

Nystagmus Retractorius

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The Koerber-Salus-Elschnig Sylvian aqueduct syndrome [1] consists of the following findings:

1. Paresis of vertical gaze
2. Pupillary abnormalities
3. Tonic spasm of convergence on attempted upward gaze
4. Clonic convergence movements, or convergence nystagmus
5. Nystagmus retractorius
6. Vertical nystagmus on gaze up or down
7. Extraocular muscle pareses

This is a report of two recently encountered cases of this rare entity in which nystagmus retractorius was associated with retraction of the upper lids. A unique optokinetic response, which to our knowledge has not been reported, was present in both patients.

Report of Cases

CASE 1.—This 60-year-old white woman was seen through the courtesy of the neurology service at the Lemuel Shattuck Hospital. Except for asymptomatic hypertension for many years, she was in good health until Feb. 10, 1959, when she suddenly developed a headache at work and her eyes were noted to turn in. She rapidly became stuporous and was hospitalized elsewhere. Examination there revealed a blood pressure of 230/160, bilateral Babinski responses, and a total bilateral ophthalmoplegia. Changing eye signs were noted thereafter. She has no recall of events from the onset of her illness to the time she entered the Lemuel Shattuck Hospital, seven weeks later. Her mental status progressively cleared. Neurological examination revealed a left hemiparesis, with the leg slightly more affected than the arm. Some diminution in position sense was noted on the left, but this was insufficient to account for the hemitremor and ataxia which were present on the left. Ophthalmologic examination revealed 20/20 vision in both eyes and normal central fields to 3/1,000 white. The most striking feature was a staring expression due to extreme bilateral lid retraction. This was constant and accompanied by infrequent blinking. There was anisocoria, with the right pupil 2.5 mm. and the left 3.5 mm., and both reacted to light. Bell's phenomenon was absent bilaterally. There was a complete palsy of upward gaze on command, and yet the eyes elevated well both on following movements and on passive movements of the head (doll's-head phenomenon). On attempting elevation to command, a marked tonic convergence spasm would occur, followed by a nystagmus retractorius, which was more marked in the left eye. There was no nystagmus in the primary position, but a slow mixed rotary-vertical nystagmus was present at times on downward gaze. Dextroversion and depression of the eyes were full and normal. Levoversion was essentially full, but a rotary nystagmus, slow and of small amplitude, with rapid phase to her left, was occasionally noted in this field of gaze. Convergence was intact. The corneal reflexes and fundi

Submitted for publication May 21, 1959.

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This work supported in part by Special Traineeship BT 357, National Institute of Neurological Diseases and Blindness (Dr. Smith); Clinical Fellow in Cerebrovascular Disease, Department of Neurology, Massachusetts General Hospital (Dr. Zieper); Heed Fellow in Ophthalmology, Massachusetts Eye and Ear Infirmary (Dr. Gay).

were normal. Examination of the eyes was otherwise within normal limits but for the optokinetic responses. On rotating targets to both sides, intact and equal horizontal responses were seen. However, a unique response was noted with vertical optokinetic stimuli. An intact response occurred to targets rotating up, but with targets rotating down, the rapid phase was replaced by the onset of convergence and retraction nystagmus. It is of interest that these defects of ocular motility were noted over two months after the onset of her cerebral vascular accident and that otherwise the patient was convalescing satisfactorily.

CASE 2.—This 72-year-old white man was seen through the courtesy of Dr. Hugo Moser. He was admitted to the Massachusetts General Hospital because of intermittent diplopia and dizzy spells for two years. Hypertension had been known for seven years. Approximately three years ago, he first became aware that although he could hear a truck approaching from the left, he could not see it. Two years ago, while driving to work, he had noted that approaching cars were double at distance but single at near. This diplopia cleared in a few days, but a similar transient episode occurred eight weeks prior to entry. For about six months dizziness was noted, and for four months he had midfrontal pressing headaches. For some time he had noted a tremor of the left arm when reaching for objects like a cup of coffee, although he is generally right-handed. The patient was emphatic that his difficulty seeing to the left preceded the onset of diplopia. He denied vertigo, blackouts, convulsions, loss of consciousness, paresthesias, weakness, and tinnitus.

The past history revealed that 40 years ago he had a penile chancre, and was then treated with bismuth injections for six years. However, serologic tests for syphilis were negative seven years prior to the present illness.

On examination, the blood pressure was 160/100 and the right carotid pulse was diminished. Neurological examination revealed some evidence of spatial disorientation and right-left confusion but no other consistent abnormalities.

On ophthalmologic examination, the visual acuity was 20/30 in both eyes. In contrast to the former patient, whose staring expression was accompanied by infrequent blinking, this patient blinked excessively. Slight retraction of the upper lids, less in degree than in the first patient, was present. The pupils were 2.5 mm. in both eyes and reacted sluggishly to light. Visual field examination revealed a congruous left homonymous hemianopia, denser below, and sparing fixation. The striking defect was in ocular motility. A total paralysis of upward gaze was present, and no elevation of the eyes occurred on command, following, passive head movements, closure of the lids, or with optokinetic stimuli. Dextroversion and depression of the eyes were full, but in contrast to the first case, there was no nystagmus on downward gaze. There was slight hesitancy on looking to the left, but the significance of this was difficult to assess because of the left-sided field defect. On attempting elevation, tonic spasm of convergence with convergence nystagmus accompanied by nystagmus retractorius occurred. Optokinetic testing revealed a similar response to the first patient. Thus, the horizontal responses were equal and intact. However, on rotating targets up, although the eyes could not be elevated above the midline, an intact response occurred. On rotating targets down, as in the first patient, nystagmus retractorius was made manifest. Ophthalmodynamometry revealed the following findings:

	Right Eye	Left Eye
Supine	110/55	150/55
Erect	62/39	110/55

The eye examination was otherwise within normal limits. The impression was Sylvian aqueduct syndrome, old right posterior cerebral artery occlusion, ophthalmodynamometric evidence of right carotid insufficiency, and hypertensive vascular disease.

Comment

The importance of the Sylvian aqueduct syndrome lies in its proven localizing significance. Salus,[2] in 1913, reported a case of nystagmus retractorius in which a cysticercus cyst was found near the aqueductal region. Askenasy[3] et al., in 1953, reported a patient similar to our first patient, in which nystagmus retractorius was associated with retraction of the upper lids and in which carotid arteriography disclosed a mesencephalic arteriovenous malformation. Kestenbaum[1] has emphasized that the ocular findings in this disorder constitute a definite clinical syndrome.

Two features appear of unusual interest in the cases here reported: (1) lid retraction and (2) optokinetic response. Retraction of the upper lids has been noted with midbrain lesions above the posterior commissure.[4] Although lid retraction may be seen with paralysis of upward gaze, the two are not invariably associated, as is seen from our first case, in which the lid retraction was present in both elevation and depression of the eyes and in which elevation of the eyes could be induced by following movements and passive rotation of the head without altering the lid retraction.

The intact horizontal optokinetic responses in these case are, in our experience, consistent with a high midbrain localization. With lesions of the pons and lower brain stem impairment of optokinetic responses is the rule. The fact that the retraction nystagmus could be elicited by vertical optokinetic stimuli (with targets rotating down) is intriguing. It is of interest that latent nystagmus and horizontal congenital nystagmus may at times be similarly made manifest by vertical optokinetic stimuli. The dissociation of command and following movements of vertical gaze in these cases may be a related finding. Thus, loss of the rapid phase up with retention of the rapid phase down, as seen in the first patient, suggests impairment of descending frontal optomotor pathways. Likewise, the retention of following movements suggests that the descending occipital optomotors may be intact. This would imply a most discrete neuropathological lesion high in the subthalamic region. The association of hemitremor and ataxia on the side of a hemiparesis in both of the present cases is somewhat reminiscent of Benedikt's syndrome and appears consistent with a localization in the mesencephalic tegmentum near the red nucleus. Certain features in the first patient resembled Parkinson's syndrome. The staring, expressionless face, accompanied by infrequent blinking, stood in striking contrast to the almost incessant blinking in the second patient.

The mechanism of nystagmus retractorius is of interest. A disjunctive, spasmodic nystagmus of convergence has been proposed as one explanation. Salus pointed out that in his patient retraction and slight adduction of both globes occurred without contraction of the pupil, and he considered this somewhat against a primary nystagmus of convergence. On the other hand, a simultaneous dyssynergic firing of all the extraocular muscles, producing posterior displacement of the globes, has also been considered. It appears that definite evidence for the mechanism of this phenomenon awaits further investigation. It is a syndrome of clinical usefulness as a discrete localizing sign.

Summary

Two cases of the Sylvian aqueduct syndrome, in which nystagmus retractorius was associated with lid retraction, are reported. A unique optokinetic response, which to our knowledge has not been previously reported, was noted.

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REFERENCES

1. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1946.

2. Salus, R.: On Acquired Retraction Movements of the Eyes, Arch. Ophth. 42:34-44, 1913.

3. Askenasy, H.; Wijsenbeek, H., and Herzberger, E.: Retraction Nystagmus and Retraction

of Eyelids Due to Arteriovenous Aneurysm of Midbrain, A.M.A. Arch. Neurol. & Psychiat. 69: 236-241, 1953.

4. Collier, J.: Nuclear Ophthalmoplegia, with Especial Reference to Retraction of the Lids and Ptosis and to Lesions of the Posterior Commissure, Brain 50:488-498, 1927.

5. Lyle, D. J., and Mayfield, F. H.: Retraction Nystagmus: A Case Report, Am. J. Ophth. 37:177-182, 1954.

6. Elschnig, A.: Nystagmus retractorius, ein Cerebrales Herdsymptom, Med. Klin. 9:8-11, 1913.

7. Koerber, H.: Über drei Fälle von Retraktionsbewegungen des Bulbus (Nystagmus retraktorius), Ophth. Klin. 7:65-67, 1903.

Abnormal Serum Proteins and Retinal Vein Thrombosis

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In recent years, interest in the normal chemistry and physiology of the blood proteins, that is, albumin and the globulins, has increased tremendously as newer more refined techniques of study of the physicochemical nature of these important body constituents have become available. Concurrently, much interest has been aroused in the pathologic physiology of proteins. Some disease states, such as multiple myeloma, are primarily characterized by the presence of abnormal proteins in the serum. In other diseases, e.g., lupus erythematosus and the collagen group, rheumatoid arthritis, lymphosarcoma, and Boeck's sarcoid, abnormal proteins are being searched for and found as manifestations or causes of these various disease entities.

Waldenström's macroglobulinemia is a recently recognized disease characterized primarily by the presence of abnormal proteins in the serum. Three patients with this disease will be presented, each of whom showed major disorders of the retinal veins presumably as a direct consequence of the abnormal properties of their proteins. The relationship of these abnormal serum proteins to the pathogenesis of retinal vein thrombosis will be discussed and illustrated with case reports and pathological specimens. The implications of this relationship will also be considered.

Technique of Serum Protein Electrophoresis

A brief review of the technique of serum protein electrophoresis will serve to clarify the distribution and definition of the serum protein components. The method of protein electrophoresis was developed in 1937, by Tiselius,[1] who sought to separate the serum protein components more qualitatively than had been accomplished by the fractionation method of Howe.[2] Tiselius' technique is based upon the fact that each protein component possesses a characteristic electrical charge. When the serum is placed in an electrical conductive solution the proteins migrate at different rates of speed according to their individual electrical charge.

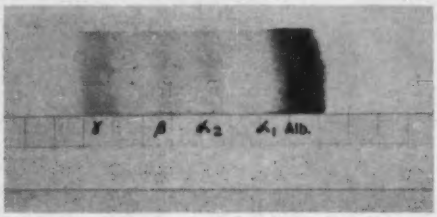

Fig. 1.—A typical normal serum electrophoretic pattern on filter paper stained with bromphenol blue.

The method as practiced in most laboratories today consists of placing a drop of serum on filter paper soaked in an electrolyte solution through which passes an electrical current. The proteins commence to migrate along this filter paper at various rates of speed. After approximately 18 hours, the filter paper is removed from the electrical field and dried in order to fix the protein components in the areas to which they have migrated. The filter paper (Fig. 1) is then stained with a dye, bromphenol blue, which combines with and stains the proteins. The density of the staining reaction is dependent upon the amount of protein present and thus represents a quantitative as well as qualitative separation.

Submitted for publication June 2, 1959.

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Five protein fractions are found in normal human serum: albumin (60%-70% of the total proteins); α_1-globulin (2%-5%); α_2-globulin (5%-10%); β-globulin (8%-12%); and γ-globulin (10%-15%).[3] The distribution of these components along the strip of filter paper is amazingly uniform corresponding to their specific net electrical charge. The stained bands of protein fractions may then be converted into the more familiar graphic form by means of a photoelectric cell analyzer. This instrument simply scans the filter paper and converts the density of the individual bands and their width into graphic curves of varying sizes (Fig. 2). The area under each curve represents the percentage of the total protein for that fraction. By measuring the total protein the amount of each fraction in grams percent can then be determined. In addition, the homogeneity of each fraction can be evaluated from the shape of the curves.

It is interesting to note that the Howe method of simple fractionation of the proteins into albumin and globulin gives a false picture of the protein components as they are now defined by electrophoresis. In the "salting out" of the Howe method, significant amounts of the β-, α_2-, and α_1-globulins were included in the albumin fraction thereby giving a falsely high value to the albumin fraction and a falsely low value to the globulin fraction.[3]

The technique of serum electrophoresis is relatively simple, requires little time, and is extremely reliable. Most hospitals and clinical laboratories today have the apparatus required for these determinations.

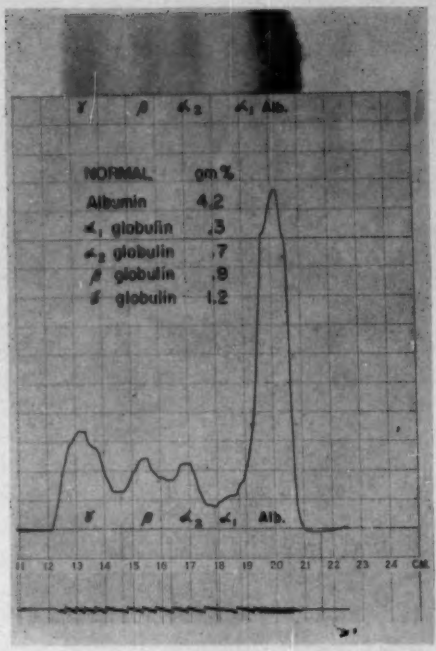

γ β α2 α1 Alb.
NORMAL gm %
Albumin 4.2
α1 globulin .3
α2 globulin .7
β globulin .9
γ globulin 1.2
γ β α2 α1 Alb.
11 12 13 14 15 16 17 18 19 20 21 22 23 24 CM.

Fig. 2.—A typical normal serum electrophoretic pattern on filter paper. Photoelectric scanning pattern appears below the corresponding stained pattern. Average normal values for the five components of the serum proteins are shown.

Waldenström's Macroglobulinemia

In 1944, Jan Waldenström, a Swedish physician, described a disease which he called macroglobulinemia characterized by the presence of an increased globulin fraction in the serum.[4] This fraction is usually in the gamma range, and is composed predominantly of large molecular size and heavy molecular weight globulins. The disease is rare, but cases are being recognized in increasing numbers as the techniques for establishing the diagnosis become more readily available. The disease seems to occur more often in males and usually commences in the fifth to seventh decades.

Waldenström's macroglobulinemia is characterized clinically by weakness, bleeding mucous membranes, hepatosplenomegaly, lymphadenopathy, and in some cases major retinal vein disease. The course of the disease is variable with a poor long term prognosis. The differential diagnosis includes multiple myeloma, lymphosarcoma, and chronic lymphatic leukemia.

The etiology of macroglobulinemia is obscure. Postmortem and biopsy studies often reveal lymphoid infiltration and reticuloendothelial proliferation in the bone marrow, spleen, and lymph nodes.[5,6] It is assumed that these infiltrates manufacture

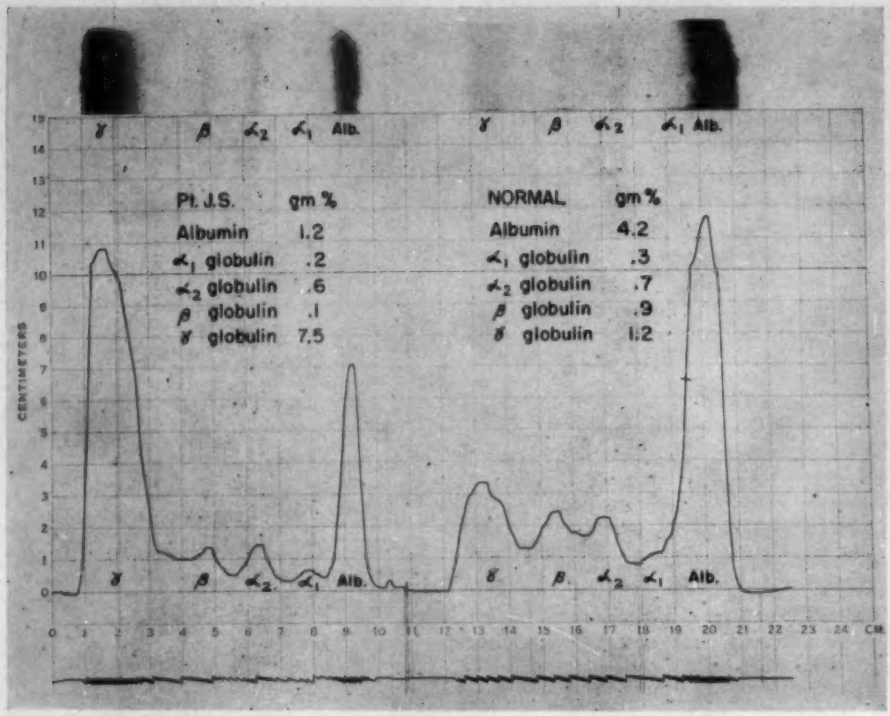


Fig. 3.—Serum electrophoretic study of a patient with Waldenström's macroglobulinemia and a comparison normal study. The large γ-globulin component corresponds to the dense staining area on the filter paper and represents the macroglobulins.

the macroglobulins, however, in vitro evidence of this is lacking. Macroglobulinemia seems to be a primary disturbance in the reticuloendothelial system and may represent a transitional or end stage in the spectrum of reticuloendothelial proliferative disorders. Some authors,[7] therefore, prefer to describe the complex as a syndrome rather than a disease entity. Increased amounts of macroglobulins have been found in association with other diseases, e.g., rheumatoid arthritis,[8] lupus erythematosus,[9] nephrosis,[9] "atypical lymphatic hyperplasia,"[10] and congenital syphilis.[11] However, the clinical and pathological findings differ from Waldenström's disease, and the formation of macroglobulins in these diseases may be considered a form of nonspecific secondary macroglobulinemia.

Therapy has been based on the similarity of macroglobulinemia to chronic lymphatic leukemia and reticuloendothelial proliferative disorders. Urethane, splenectomy, radioactive phosphorus, and cortisone have been tried without success.[12,13] Replacement of whole blood when necessary remains the most effective supportive measure.

The laboratory findings in macroglobulinemia include a characteristically high elevation of the erythrocyte sedimentation rate.[14] Lymphocytosis and a moderate anemia may or may not be present.[15] The urine is usually normal. X-ray findings are usually unremarkable, although pathologic fractures have been reported.[16] There may be numerous defects in the clotting mechanism ranging from thrombocytopenia,[17] to prolonged prothrombin time, and AC-globulin deficiency.[18] Hyperglobulinemia is the most important finding and this is usually noted as a sharp tall peak in the γ-globulin range on the electrophoretic pattern

WALDENSTROM'S MACROGLOBULINEMIA

	J.S. PH/997509	S.F. PH/74821	B.H. PH/175930
AGE	60	62	48
SYMPTOMS			
Bleeding from mucous membranes	Present	Present	Present
ABNORMAL PX.			
Hepatomegaly	Present	Present	Present
Splenomegaly	Absent	Present	Present
Lymphadenopathy	Present	Present	Present
Fundus:			
a) Engorged retinal veins			Present
b) Diffuse retinal hemm.		Present	
c) Retinal vein thrombosis	Present		
LABORATORY DATA			
Elevated ESR(mm./hr)	100	157	70
Hyperglobulinemia(gm%)	4.8-8.4	4.5-8.5	5.2-5.3
Serum Ultracentrifugation (presence of macroglobulins i.e. sedimentation constant of S_{15} or greater)	S_{26}	S_{20}	S_{20}
Lymphocytosis in blood	41%	48-90%	60%
Lymphocytosis in bone marrow	Not done	Present	Present
Platelets(may be reduced)	Normal	Normal	Normal
COEXISTENT DISEASE	Rheumatoid Arthritis	None	None

Fig. 4.—Summary of the laboratory and clinical data.

(Fig. 3). Occasionally, this peak has the mobility of the M (myeloma) protein or the β-globulin.[13]

To establish a definitive diagnosis of macroglobulinemia, the presence of the extremely high molecular weight globulins must be demonstrated by laboratory methods. A relatively simple test is the water dilution test (Sia water test).[19] One drop of the patient's serum is pipetted into a glass cylinder filled with distilled water. A slight haziness develops with normal serum and this is considered a one plus reaction. When a heavy precipitate forms, which settles rapidly to the bottom of the cylinder, it is considered a positive test for macroglobulins. This test, however, is not always positive even with large amounts of macroglobulins present in the serum and at best is a fairly accurate screening device. The only definitive method of demonstrating the presence of macroglobulins is by selectively separating them from the remainder of the serum by ultracentrifugation.

In the ultracentrifuge the serum is spun at 58,000 times per minute, and through a complex system of optics and high speed photography the rate of settling of the different molecular weight components is recorded.[20] The rate of sedimentation is defined by the Svedberg (S) unit. The sedimentation constants for normal serum in an ultracentrifugal field are S 4.5 for the albumin, and S 7.0 for the γ-globulin corresponding to a molecular weight of approximately 65,000 for the albumin and 150,000 for the globulin. The macroglobulins have sedimentation constants ranging from S 15 to S 26 corresponding to molecular weights of approximately 600,000 to 1,000,000 or greater. Lower sedimentation constants of 12.7 and 11.7, however, have been described in macroglobulinemia.[18,5] Normal serums may have a small amount of macroglobulins; however, any amount greater than 5% is considered pathologic.[21]

Recent work[22] suggests that hydrolysis of macroglobulins yields normal γ-globulins. Thus, the macroglobulins may actually represent high molecular weight polymers of low molecular weight normal γ-globulin. Immunologic studies of the macroglobulins have revealed that the pathologic macro-

Fig. 5.—(Case 1) Fundus drawing O.S. Dilated and tortuous retinal veins without hemorrhages or exudates. Optic disc and macula normal. Right eye has similar changes.

globulins in macroglobulinemia are antigenically specific.[23,24] In addition, Pedersen[21] found that the pathologic macroglobulins have physicochemical properties which differ from the small amounts of normally occuring high molecular weight globulins. The entire question of whether the macroglobulins represent merely an increased amount of normal proteins or represent qualitatively different proteins (dysproteinemia) is still under discussion and study.

Ophthalmological Findings in Waldenström's Macroglobulinemia

Three patients with proven macroglobulinemia of Waldenström will be presented each revealing a different phase of retinal venous disorders associated with this disease. The fundoscopic spectrum includes dilatation and tortuosity of the veins, peripheral venous thrombosis and hemorrhage, and central or branch retinal vein occlusion. These changes appear to represent a pathogenetic sequence of events directly attributable to the abnormal characteristics of the serum proteins.

A brief summary and a discussion of each case follows. The pertinent data are included in Figure 4.

Case 1.—A 48-year-old Negro female was admitted to Presbyterian Hospital in December, 1957, complaining of persistent bleeding from a tooth socket. Physical examination revealed splenomegaly and bleeding from a tooth socket which was difficult to control. There were no ocular complaints and the fundi were described as normal. Laboratory examination revealed an erythrocyte sedimentation rate of 55 mm per hour, hemoglobin 11 gm., and total protein 8.0 gm. (albumin 2.7 gm., globulin 5.3 gm., with γ-globulin of 3.5 gm.). The bleeding was controlled finally, and the patient discharged with no specific diagnosis.

In April, 1958, the patient complained of persistent nose bleeds. Laboratory examination at this time included an ultracentrifuge study of the serum which revealed a large component of macroglobulins of S 15 and greater. Diagnosis of Waldenström's macroglobulinemia was thus established.

In August, 1958, the patient still had no ocular complaints. Visual acuity with correction was 20/30 O.U. Visual fields were normal. External examination was normal, muscle balance was good, and the intraocular tension (Schiøtz) was normal. The media were clear. Both fundi revealed considerable dilatation, and tortuosity of the retinal veins extending out into the periphery. The arterioles, maculae, and optic discs appeared normal. There were no hemorrhages or exudates. A fundus drawing was made (Fig. 5).

In December, 1958, the patient noted visual blurring in the left eye. Superficial linear hemorrhages were noted near both optic discs, the venous tortuosity had increased, the discs remained flat, and the arterioles normal. On December 28, 1958, the patient expired from what appeared to be a cerebral thrombosis. Autopsy permission including the eyes was obtained.

The main clinical and laboratory findings in this case are summarized in Figure 4. The electrophoretic pattern (Fig. 6) made six weeks before the patient's death reveals

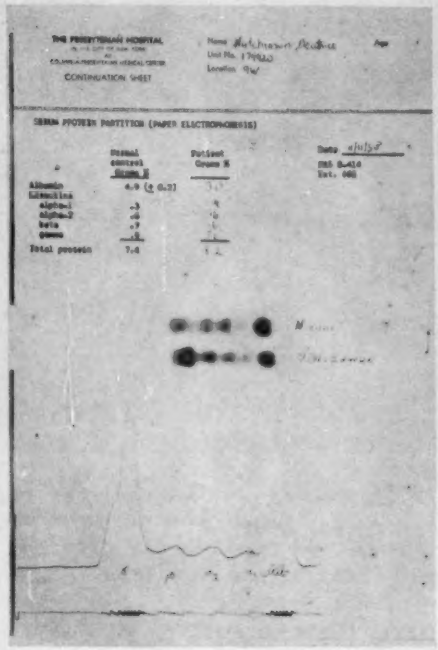


Fig. 6.—Serum electrophoretic study of Case 1. The macroglobulins migrate with the gamma globulin component creating a tall peak in the gamma globulin range.

the large spike in the γ-globulin range, representing the large amounts of macroglobulins present.

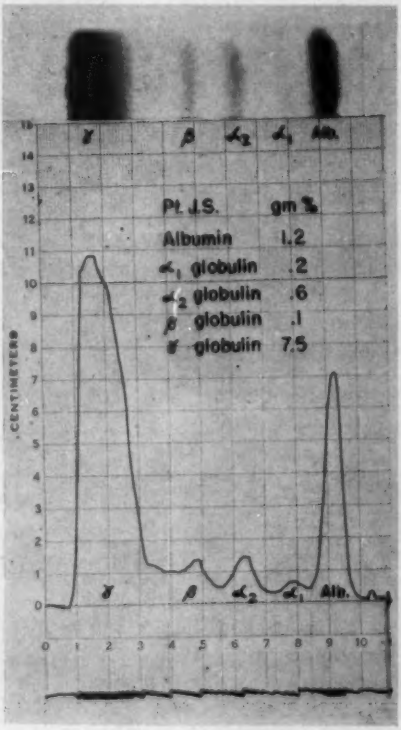
The striking dilatation and tortuosity of the retinal veins have been noted by other authors.[25,26] A recent report[27] also described visual difficulties associated with the venous dilatation, although the patient had no ocular complaints until the retinal hemorrhages appeared. The visual complaints seem to reflect the vascular insufficiency found in cases of impending retinal vein obstruction where dilatation of the retinal veins is a prominent finding before the appearance of hemorrhages.[28]

The patient did not have any demonstrable arteriosclerotic disease, congestive heart failure, or increased peripheral venous pressure. The anemia was mild and there was no evidence of increased intracranial pressure. The fundi revealed no changes suggestive of sclerosis or phlebitis. In the absence of these well defined etiologically significant entities, the explanation of the patient's retinal venous disorder must be sought elsewhere.

Case 2.—A 62-year-old white female was seen in May, 1954, with a two year history of anemia, recurrent epistaxes, hepatomegaly, and splenomegaly. The working diagnosis throughout the patient's illness was chronic lymphatic leukemia. Initial fundus examination was essentially normal and the patient had no visual complaints. Laboratory examination revealed an erythrocyte sedimentation rate of 157 mm. per hour, hemoglobin 6 gm., platelets 200,000, and a white blood cell count of 10,600 with 71% lymphocytes. Total protein was 7.7 gm. (albumin 2.9 gm., globulin 4.8 gm.).

The patient was treated with blood transfusions; however, it was difficult to find a compatible donor. One month prior to

Fig. 7.—Serum electrophoretic study of patient Case 3.



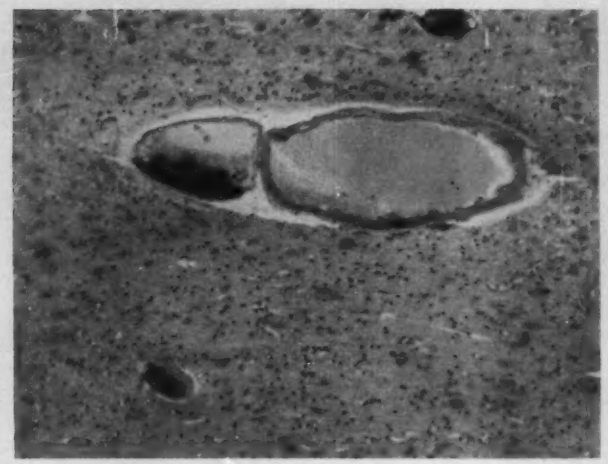


Fig. 8.—(Case 2) Cerebral venule. Deposits of homogeneous eosinophilic material in the lumen. Hematoxylin and eosin; ×120.

death, the patient complained of diminution of vision. Fundoscopic examination revealed bilateral small punctate retinal hemorrhages. The patient lapsed into coma after a progressive downhill course and died within twenty-four hours in December, 1955. Postmortem examination exclusive of the eyes was performed.

It is of interest that this patient died with a diagnosis of chronic lymphatic leukemia. After death, however, two new pieces of evidence developed which radically changed this diagnosis. First, a serum drawn antemortem was ultracentrifuged and revealed a large component of S 20 macroglobulins. Second, the postmortem examination failed to show the expected changes of lymphatic leukemia. Instead, the dominant cell type was lymphocytes with scant cytoplasm, with transitional forms to plasma cells satisfying the morphologic criteria of Waldenström's macroglobulinemia.[9] The lymphocytosis noted during life represented the accumulation of peripheral lymphocytes occasionally found in macroglobulinemia.[15]

The ocular finding of multiple retinal hemorrhages is the one most commonly reported in the medical literature on macroglobulinemia. Quattrin et al. reported on three personal cases and reviewed sixteen well documented cases of macroglobulinemia.[20] Six of these nineteen cases had retinal hemorrhages. Unfortunately, descriptions of the eyegrounds are all too brief and incomplete, and several authors do not mention any fundoscopic examination. Ferriman and Anderson[15] reported on one case well documented with ultracentrifugation whose only symptom of macroglobulinemia was visual blurring. The fundus drawing accompanying the article reveals multiple small retinal hemorrhages in addition to marked tortuosity and dilatation of the retinal veins. The fundus picture suggests thrombosis of the smaller peripheral venules without involvement of the central vein or its major branches.

Case 3.—A 60-year-old white male was followed in the outpatient department of Presbyterian Hospital since 1950 for rheumatoid arthritis involving the hands, wrists, elbows, and shoulders. The patient had no visual complaints or fundus abnormalities when first seen. The initial laboratory data revealed an erythrocyte sedimentation rate of 112 mm per hour, hemoglobin 13 gm., and normal white blood cells with a normal differential count. Total protein was 7.7 gm. (albumin 3.2 gm.; globulin 4.5 gm. by the Howe method). The patient was treated for his arthritis with gold injections and steroids. It was felt that the

Fig. 9.—(Case 2) Cerebral venule. Red blood cells clustered near vessel wall. Large amount of eosinophilic material in lumen. Hematoxylin and eosin; × 430.

increased serum globulin resulted from the rheumatoid arthritis.

In July, 1955, it was found that the total protein (Howe method) had risen to 9.1 gm. with albumin 2.8 gm., and globulin 6.3 gm. Serum protein electrophoresis was performed for the first time in September, 1955, and this demonstrated an extremely large component with the electrophoretic mobility of the γ-globulin (Fig. 7). In December, 1955, ultracentrifugal analysis of the patient's serum revealed the presence of a macroglobulin with a sedimentation constant of S 26, and a second abnormal component of S 13.

No specific therapy was instituted for the macroglobulinemia since the patient was asymptomatic. The first symptom of macroglobulinemia developed in May, 1956, when the patient consulted his private ophthalmologist * because of sudden loss of vision in the right eye. Visual acuity was O.D. 20/200; O.S. 20/25. The right fundus revealed engorged veins and a thrombosis of the lower temporal retinal vein with hemorrhages and exudates. The left fundus had tortuous retinal veins with a thrombosis of the upper nasal vein with several small hemorrhages. It is of interest that six years previously, during a routine refraction, the patient's ophthalmologist noted that the

* Dr. G. Mueller who kindly permitted use of her private records on this patient.

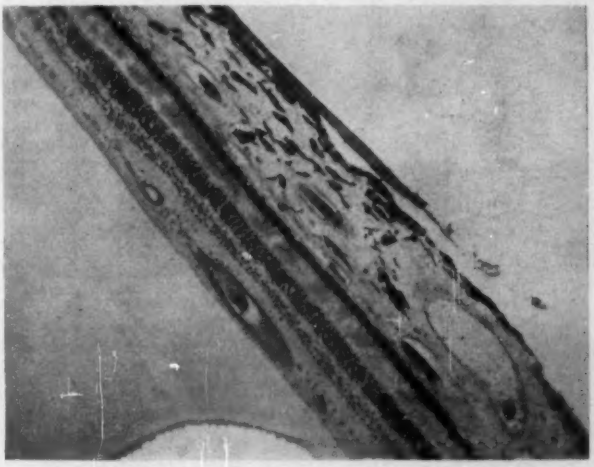


Fig. 10.—(Case 1) Peripheral retinal vein. Dark staining material in lumen is PAS positive protein. Periodic acid-Schiff; Left eye; × 120.

veins in both fundi were unusually tortuous and congested.

In June, 1956, one month after the initial ocular complaint, it was noted that the lower nasal retinal vein of the left eye had thrombosed. Thereafter, no new hemorrhages were noted and the hemorrhages slowly absorbed with improvement of the visual acuity of the right eye to 20/50.

On the final hospital admission in July, 1956, hepatomegaly was noted for the first time. The total protein had increased to 11.3 gm. with a distinct increase in the abnormal γ-globulin constituent. On August 12, the patient was awakened by an excruciating headache. In the course of one hour he rapidly became comatose and expired. Permission for postmortem examination was not obtained.

This case represents retinal vein disease as the only symptomatic manifestation of Waldenström's macroglobulinemia in an otherwise healthy individual. The association of macroglobulins with rheumatoid arthritis has been noted by Svartz [8]; however, whether a causal relationship exists is not known.

Danis et al. comment on the appearance of retinal vein thrombosis in one patient with macroglobulinemia which they consider characteristic of the disease.[30] Cagianut and Hoffmann-Egg [26] have reviewed the ocular findings in macroglobulinemia. They suggest three clinical varieties of macroglobulinemia which differ in the ocular findings. These are: (*a*) chronic purpura of the skin not associated with ocular changes, (*b*) extensive bleeding of mucous membranes often associated with retinal hemorrhages, and (*c*) central nervous system disturbances often associated with retinal hemorrhages and venous congestion. These authors present four case reports, all of which showed retinal vein thrombosis or hemorrhages. However, only one of the cases was documented as macroglobulinemia with an actual demonstration of macroglobulins in the serum. The three patients presented here appear to fall into the Groups b and c cited by Cagianut. Two of the patients, Cases 1 and 2, had extensive mucous membrane bleeding, and all three patients had terminal events related to cerebrovascular insults.

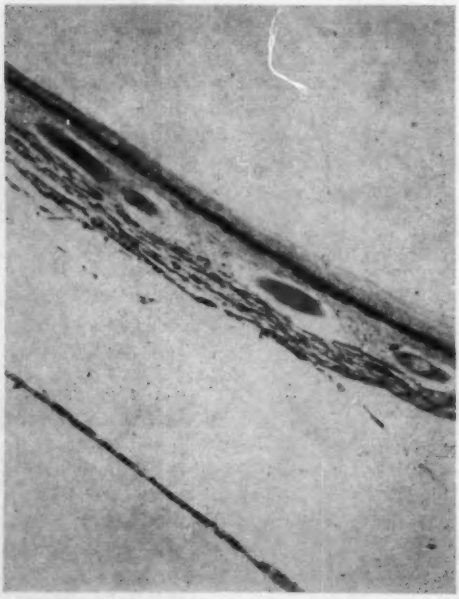


Fig. 11.—(Case 1) Choroidal blood vessels. Dark-staining material in lumina in PAS fixation. Periodic acid-Schiff; right eye; × 100.

Group a, as cited by the authors, is actually not a form of macroglobulinemia, but rather a different disease entity called, "Purpura Hyperglobulinemica," by Waldenström.[9] It is a chronic relapsing purpura of the skin associated with an increased γ-globulin component without abnormal amounts of macroglobulins.

Pathophysiology of Retinal Vein Disorders in Macroglobulinemia

The sequence of events in the fundi of the three patients presented seems to reveal a pathogenetic sequence in the development of retinal vein thrombosis. The first patient initially showed only dilatation and tortuosity of the retinal veins. The second patient revealed multiple superficial punctate hemorrhages. Finally, the third patient had a history of unusually dilated retinal veins without ocular symptoms and several years thereafter developed branch vein occlusions. Cases already cited from the literature reveal the association of macroglobulinemia with retinal vein disorders. Circumstantially a causal relationship seems evident. However, more common etiologic explanations must be considered first.

Atherosclerosis of the arteriole, or venous walls, or both is the etiologic mechanism in most cases of retinal vein thrombosis.[31] The histopathology of macroglobulinemia fails to show any specific sclerotic involvement of vessel walls, and two of the patients, Cases 1 and 3, failed to show any fundoscopic or systemic evidence of atherosclerosis. The third patient, Case 2, unfortunately had inadequate descriptions of the fundi. Phlebitis,[31] another well documented cause of venous thrombosis, was not present in any of the patients. Neither polycythemia, diabetes, nor leukemia were found in these patients. These entities are also known to produce venous dilatation and congestion leading to retinal vein thrombosis.[32,33,34] Therefore, in the absence of overt vascular sclerosis, inflammatory diseases of the vessels, or blood dyscrasias, another explanation must be sought to interpret the venous changes. The only apparent remaining explanation is stagnation of the blood flow. Stagnation and slowing of the blood stream may lead first to dilatation and tortuousity of the affected venous tree, secondly to small vein thrombosis with hemorrhages, and finally, to major branch or central retinal vein occlusion.

This hypothesis is supported by the abnormal physical characteristics of the serum proteins in macroglobulinemia and by histopathologic evidence. An outstanding characteristic of the patient's serum in macroglobulinemia is the extreme viscosity.[35] Difficulty is often encountered in

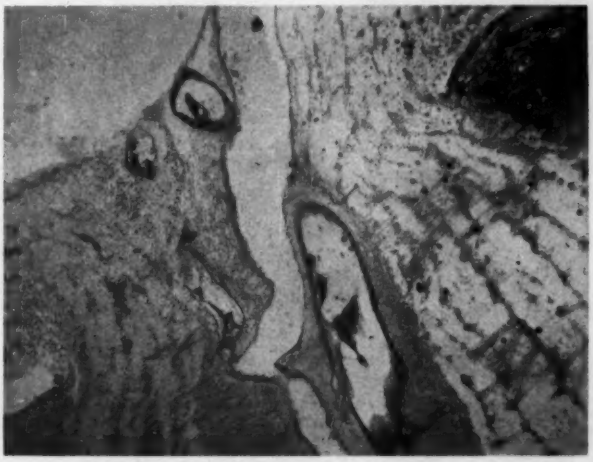


Fig. 12.—(Case 1) Optic nerve. Dilated central retinal vein. PAS positive material intraluminally. Note red blood cells do not stain with PAS. Periodic acid-Schiff; Left eye; × 60.

withdrawing blood from the veins, and occasionally, the serum will gel in the syringe even in the absence of cryoglobulins which are rarely found in association with macroglobulinemia.[9] Increased serum viscosity results in a physical modification of the blood which leads to a decrease in the velocity of the blood stream. As the velocity of the blood decreases the lateral pressure of the blood upon the vein wall increases. The thin-walled veins respond to this increased pressure by dilatation and tortuosity. Persistence of this stasis in the venous tree may eventually lead to thrombosis of the smaller venules followed by the larger venous branches. The thrombosis which is seen clinically is particularly remarkable in view of the frequent finding of clotting defects in patients with macroglobulinemia. We can postulate, therefore, that the stasis induced by the hyperviscosity of the serum is so extreme that it overcomes the anticoagulant tendency, if present, to inhibit thrombosis.

The pathologic data available from the patients, Cases 1 and 2, appears to support the contention that venous stasis and thrombosis result from excessive amounts of viscous proteins in the blood stream. Many of the patients with macroglobulinemia at autopsy reveal multiple cerebral thrombi with hemorrhagic extravasation. Again this pattern of thrombosis may occur despite dysfunction of the patient's clotting mechanism.

Postmortem examination of the brain of Case 2 (the eyes were not obtained) revealed a heavy deposition of a homogeneous eosinophilic substance in the lumen of the smaller cerebral arterioles and venules. A section of a cerebral venule comparable in size to the central retinal vein is shown in a hematoxylin and eosin preparation in Figure 8. This amorphous material was positive for the periodic acid-Schiff (PAS) stain indicating the presence of a glycogen bound protein. In macroglobulinemia the glycoprotein content of the blood is increased comparable to the increase of the globulins, and as much of the abnormal globulin is incorporated into a polysaccharide complex.[36] Normal serum does not ordinarily take the PAS stain. Cytoplasmic inclusions in the abnormal cells found in macroglobulinemia have also been noted to take the PAS stain.[5] It is suggested that the histopathologic material represents large amounts of abnormal serum proteins coagulated intraluminally. It is speculative whether or not this is an antemortem change. However, the presence of such large amounts of protein within the vessel forcing the blood cells to the periphery of the lumen (Fig. 9) strongly suggests an in vivo situation of extreme sluggishness, or cessation of the blood flow.

Case 1, whose eyes were obtained for pathologic study, also revealed this amorphous material in the retinal veins as well as in the cerebral vessels. A section of a retinal vein near the periphery is shown filled with PAS positive material indicating the presence of large amounts of the abnormal proteins (Fig. 10). Several choroidal vessels are also shown in Figure 11. The gross dilatation of the retinal veins noted clinically (Fig. 5) can be seen microscopically (Fig. 12). This patient, as has been previously noted, had no evidence of increased intracranial pressure, papilledema, or retinal vein thrombosis. It is interesting to note that the red cells filling the vein do not stain with PAS, as has been previously reported.[37] However, this section of the optic nerve head does reveal a matrix of PAS positive material in areas of the lumen of the vein.

In the German literature, there are two pathological studies recorded of the eyes of patients with suspected macroglobulinemia of Waldenström.[26] Both patients revealed antemortem retinal vein thrombosis associated with the clinical symptomatology of macroglobulinemia. Hyperglobulinemia was present; however, the ultracentrifuge test for definitive demonstration of macroglobulins was not performed. In these strongly suspected cases, both globes revealed large amounts of eosinophilic material in the

retinal veins and in the retinal tissue which the authors concluded was the abnormal macroglobulin. The sections were not stained with the periodic acid-Schiff reagent. No comparable pathological reports have been found in the English literature and Case 1 appears to be the first well documented case of Waldenström's macroglobulinemia with a pathological examination of the eyes recorded.

Comment

The fundoscopic findings associated with Waldenström's macroglobulinemia appear to be a primary consequence of the pathology of this disease. The pathognomonic disturbance of macroglobulinemia is the production of abnormal serum proteins which are detectable by modern laboratory analysis. The physicochemical characteristics of these abnormal proteins result in mechanical blockage of the retinal venous system by means of impedance and stasis of the vascular flow. The sequence of events occurring in the fundus can thus be characterized as a retinopathy of abnormal proteins.

The recognition of the causal relationship implied by the clinical picture of engorged retinal veins, the laboratory demonstration of abnormal viscous proteins, and the pathological identification of these abnormal proteins in the retinal veins lead to new speculation about the pathogenesis of retinal vein thrombosis. Patients with retinal vein thrombosis who fail to show any clinical or laboratory evidence of the well defined causes of thrombosis present a fertile field for study. Macroglobulinemia itself is a rare disease and would not be expected to account for more than a minute percentage of cases. The normal globulins, however, especially the γ-globulin component, are often quite viscous molecules.[4] Numerous reports of increased normally occurring globulins from a variety of causes including idiopathic hyperglobulinemia are appearing in the medical literature.[3,5] Increased amounts of these globulins might induce sufficient stasis to lead to a *de novo* venous thrombosis, or as a contributing factor lead to thrombosis in a vessel already compromised by atherosclerotic changes in an adjoining arteriole or in the venous wall itself.

Hyperglobulinemia may precede the clinical manifestations of a disease, or may exist without any associated disease. The patient could therefore present only retinal venous disease without systemic pathology or symptomatology. This proposed relationship of increased serum proteins (γ-globulins) to retinal vein thrombosis is hypothetical and speculative. There have been no specific investigations of this suggested hypothesis. A retrospective case study of 100 consecutive unselected cases of retinal vein thrombosis from Presbyterian Hospital Institute of Ophthalmology is in preparation by me. This study suggests that a positive relationship between increased γ-globulin from any cause and retinal vein thrombosis does exist.

The technique of serum electrophoresis is simple and readily available. Routine electrophoretic studies in patients with retinal vein thrombosis, especially in those patients without an overt explanation for the thrombosis, would be most helpful in evaluating the validity of this suggested relationship.

The author wishes to express his appreciation to Dr. Gordon M. Bruce of the Institute of Ophthalmology, Presbyterian Hospital, who generously gave much helpful advice and criticism. He also wishes to acknowledge the assistance of Dr. Edith Sproul of the Francis Delafield Hospital, and the medical departments and record rooms of Presbyterian and Francis Delafield Hospitals. The ultracentrifuge studies were performed by Dr. C. Christian and the Protein Laboratory of Francis Delafield Hospital. The art and photography work was provided by Mr. G. Bethke, Mr. E. Gonzalez, and Mr. J. Lafayette. Mr. P. Fleischmann translated the German reference articles. The ocular pathology sections were reviewed by Drs. A. B. Reese, J. A. C. Wadsworth, and A. Forrest.

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REFERENCES

1. Tiselius, A.: A New Apparatus for Electrophoretic Analysis of Colloidal Mixtures, Tr. Faraday Soc. 33:524-531, 1937.

2. Howe, P. E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in Blood, J. Biol. Chem. 49:93-113, 1921.

3. Wall, R. L.: The Use of Serum Protein Electrophoresis in Clinical Medicine, A.M.A. Arch. Int. Med. 102:618-658 (Oct.) 1958.

4. Waldenström, J.: Incipient Myelomatosis or "Essential" Hyperglobulinemia with Fibrinogenopenia—A New Syndrome?, Acta med. scandinav. 117:216-247, 1944.

5. Zlotnick, A.: Macroglobulinemia of Waldenström, Am. J. Med. 24:461-466 (Mar.) 1958.

6. Tischendorf, W., and Hartman, F.: Makroglobulinäemie (Waldenström) mit gleichzeitger Hyperplasie der Gewebsmastzellen, Acta haemat. 4:374-383, 1950.

7. Hampton, J. W.: Waldenström's Macroglobulinemia, New England J. Med. 258:1293-1296 (June 26) 1958.

8. Svartz, N.: Macroglobulins in Rheumatoid Arthritis, Acta med. scandinav. 158:163-165, 1957.

9. Waldenström, J.: Abnormal Proteins in Myeloma, in Dock, W. and Snapper, I: Advances in Internal Medicine, Vol. 5, Chicago, The Year Book Publishers, Inc., 1952, pp. 398-440.

10. Dalgaard, E. B.: A Case of Hyper- and Macroglobulinemia Accompanied by Atypical Lymphatic Hyperplasia, Acta path. et microbiol. scandinav. 27:506-518, 1950.

11. Willi, H.; Koller, F., and Raaflaub, J.: Symptomatische Makroglobulinämie bei Lubes Congenita; Beitrag zur Frage der Fibrinasthenie Fanconi, Acta haemat. 11:316-320, 1954.

12. Wilde, H., and Hitzelberger, A. I.: Macroglobulinemia: Clinical Features and Differential Diagnosis, Blood 9:875-880 (Sept.) 1954.

13. Jim, R. T. S., and Steinkamp, R. C.: Macroglobulinemia and Its Relationship to Other Paraproteins; With a Case Report, J. Lab. & Clin. Med. 47:540-561 (Apr.) 1956.

14. Schulten, H., and Kanzow, U.: Makroglobulinämie (Waldenström'sche Krankheit), Folia haemat. 76:49-72, 1956.

15. Ferriman, D. G., and Anderson, A. B.: Macroglobulinemia of Waldenström, Brit. M.J. 2:402-403 (Aug. 18) 1956.

16. Layani, F.; Aschkenasy, A., and Bengui, A.: Macroglobulinémie avec lésions du squelette, Presse méd. 63:44-46, 1955.

17. Mackay, J. R.; Eriksen, N.; Motulsky, A. G., and Volwiler, W.: Cryo- and Macroglobulinemia. Electrophoretic, Ultracentrifugal, and Clinical Studies, Am. J. Med. 20:564-587 (Apr.) 1956.

18. Voigt, A. E., and Frick, P. G.: Macroglobulinemia of Waldenström: A Review of the Literature and Presentation of a Case, Ann. Int. Med. 44:419-425 (Feb.) 1956.

19. Sia, R. H. D.: Simple Method for Estimating Quantitative Differences in Globulin Precipitation Test in Kala-Azar, China M.J. 38:35-42 (Jan.) 1924.

20. Svedberg, T., and Pedersen, K. O.: The Ultracentrifuge, Oxford, Clarendon Press, 1940.

21. Pedersen, K. O.: Ultracentrifugal Studies on Serum and Serum Fractions, Thesis, Uppsala, 1945.

22. Deutsch, H. F., and Morton, J. I.: Dissociation of Human Serum Macroglobulins, Science 125:600-601 (Mar. 29) 1957.

23. McFarlane, A. S.; Davey, S.; Slack, H. G. B., and Papastamatis, S. C.: An Unusual Case of Hyperglobulinaemia, J. Path. & Bact. 64:335-342, 1952.

24. Habich, H.: Zur Antigenanalyse der Paraproteine bei Makroglobulinämien, Schweiz. med. Wchnschr. 83:1253-1256, 1953.

25. Korsten, H. B., and Berneaud-Kötz, G.: Ein frühes Stadium der Fundus paraproteinaemicus be einem Fall von Makroglobulinämie, Klin. Monatsbl. Augenh. 128:679-686, 1956.

26. Cagianut, B., and Hoffmann-Egg, L.: Über Augenhintergrundsveränderungen bei Makroglobulinämien, von Graefes Arch. Ophth. 153:381-406, 1953.

27. Hanlon, D. G.; Bayrd, E. D., and Kearns, T. P.: Macroglobulinemia- Report of Four Cases, J.A.M.A. 167:1817-1831 (Aug. 9) 1958.

28. Klein, B. A.: Prevention of Retinal Venous Occlusion: With Special Reference to Ambulatory Dicumarol Therapy, Am. J. Ophth. 33:175-184 (Feb.) 1950.

29. Quattrin, N.; Dini, E., and Piccoli, P.: On the Differential Diagnosis of the Purpuras with Hypergammaglobulinemia or Macroglobulinemia, Acta med. scandinav. 156:25-38, 1956.

30. Danis, P.; Brauman, J., and Coppez, P.: Les lésions du fond d'oeil au cours de certaines hyperproteinemies (Myelome, à cryoglobuline, macroglobulinemie), Acta ophth. 33:33-52, 1955.

31. Klein, B. A., and Olwin, J. H.: A Survey of the Pathogenesis of Retinal Venous Occlusion (Emphasis upon Choice of Therapy and an Analysis of the Therapeutic Results in Fifty-Three Patients), A.M.A. Arch. Ophth. 56:207-247 (Aug.) 1956.

32. Cohen, M.: Lesions of the Fundus in Polycythemia, Arch. Ophth. 17:811-818 (May) 1937.

33. Root, H. F.; Mirsky, S., and Ditzel, J.: Proliferative Retinopathy in Diabetes Mellitus, J.A.M.A. 169:903-909 (Feb. 28) 1959.

34. Culler, A. M.: Fundus Changes in Leukemia, Tr. Am. Ophth. Soc. 49:445-473, 1951.

35. Waldenström, J.: Recherchés cliniques et physicochemiques sur les hyperglobulinémies, Presse méd. 57:213-215, 1949.

36. Laurell, C. B.; Laurell, H., and Waldenström, J.: Glycoproteins in Serum from Patients with Myeloma, Macroglobulinemia, and Related Conditions, Am. J. Med. 22:24-36 (Jan.) 1957.

37. Pearse, A. G. E.: The Nature of Russel Bodies and Kurloff Bodies: Observations on the Cytochemistry of Plasma Cells and Reticulum Cells, J. Clin. Path. 2:81-88, 1949.

38. Feinstein, A. R., and Petersdorf, R. G.: The Clinical Significance of Hyperglobulinemia. I. Diagnostic Implications, Ann. Int. 44:899-924 (May) 1956.

Stain Permeability and Ultrastructure of the Corneal Endothelium

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In a previous paper [1] reference was made to difficulties encountered in studying normal corneal endothelial cells owing to the rapid development of cytoplasmic vacuoles which could only be prevented by special techniques of fixation. Since many of the descriptions in the literature are based on poorly fixed material, the normal histology has been reinvestigated and an attempt has been made to correlate the findings obtained with the light and electron microscope.

Material

It was not possible to obtain rapidly fixed human eyes; consequently, rabbit, cat, and monkey eyes were examined which had been perfused with fixative while the animal was anesthetized or very soon after death. Formalin 10% and buffered osmic acid 1% were used, the latter particularly for fixing material which was subsequently cut into small blocks and prepared for study with the electron microscope. Segments of cornea, which included the filtration angle, were inverted in a number of routine aqueous and alcoholic stains, and, after washing away excess stain, flat preparations of the endothelium and Descemet's membrane were examined. Unstained flat preparations were also examined with the phase microscope, and the absence of vacuolation was used as a criterion for adequate fixation.

Findings

Light Microscope.—Examination of tissue which had been rapidly fixed in formalin failed to show any intracellular staining except where stain diffused into a few of the cells at the cut edges of the block. The initial observations were made using hematoxylin, but it was later found that toluidine blue, polychrome methylene blue, alcian blue, colloidal iron, and PAS all failed to stain intracellular structures, which is in marked contrast to the experience of other investigators who have studied these cells. It was particularly difficult to interpret this observation because the corneal epithelium, the adjacent trabecular endothelial cells, the lens epithelium, and iris all stained in the expected manner. Subsequent observations showed, however, that when the cells were injured by trauma or if the cornea became wrinkled during fixation, resulting in vacuole formation, then the cytoplasm and nuclei took up the stains in the usual way (Fig. 1).

Although no intracellular endothelial staining occurred when hematoxylin was applied to the surface of well-fixed cornea, a hexagonal pattern of staining developed at the cell boundaries which appeared to be due to precipitation of stain between the cells. When polychrome methylene blue stain was employed a similar hexagonal staining pattern occurred, and, in addition, on focusing just below the surface of the cell an irregular pattern of staining similar to the contour lines of a map or the outline of the components in a jig-saw puzzle could be seen extending into the center of the cell. In suitable preparations near the cut edge of the corneal segment it was possible to photograph a regular hexagonal pattern at the surface of the cells, a slightly wavy hexagonal pattern just below the surface, and at a deeper level in the region of

Submitted for publication May 11, 1959.

From the Department of Ophthalmology, University of Toronto.

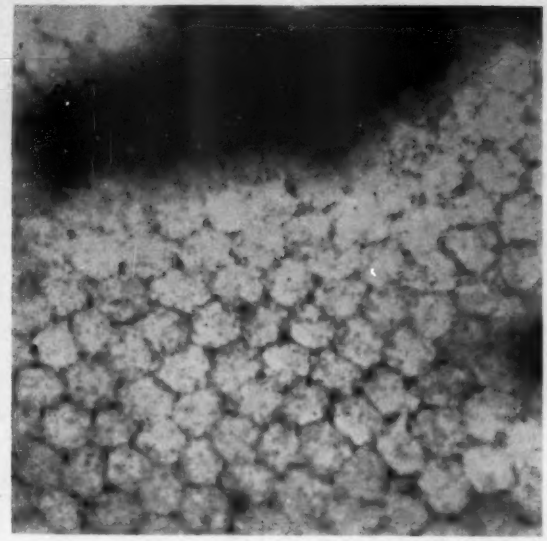


Fig. 1.—Flat preparation showing a localized area of staining where cells have undergone vacuolation and elsewhere a hexagonal pattern due to stain precipitation and penetration into the intercellular space. Cat; polychrome methylene blue; × 380.

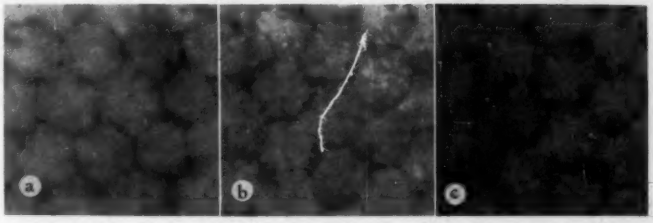


Fig. 2.—Flat preparation photographed at three levels, showing (*a*) surface precipitation of stain, (*b*) filling of channels between interdigitations, (*c*) at a deeper level, incomplete filling of channels between the cells and Descemet's membrane. Monkey; polychrome methylene blue. Reduced approximately ½ from mag. × 950.

Descemet's membrane the tortuous contour line pattern which extended completely across the cell (Figs. 2 and 3). In a few preparations the nuclear membrane took up the stain, and by careful focusing the contour line pattern could be localized deep to the nucleus next to Descemet's membrane (Fig. 4).

Further experiments were done to determine whether the polychrome stain was combining with a substance within the cells or filling a tortuous system of channels

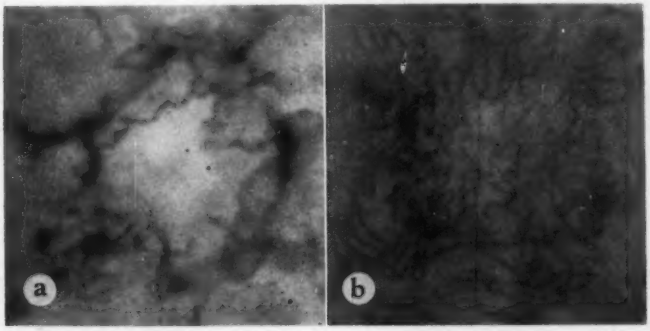


Fig. 3.—Flat preparation showing the deep channel system in greater detail. (*a*) Cat, incomplete filling; (*b*) monkey. Polychrome methylene blue. Reduced ⅛ from mag. × 1,800.

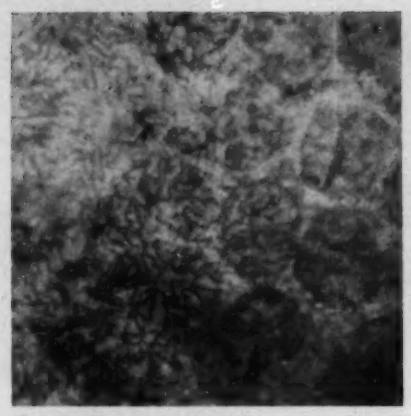


Fig. 4.—Flat preparation from the edge of a block of cornea, showing the deep channel system in relation to the cell nuclei in focus on the right. Monkey; polychrome methylene blue; × 950.

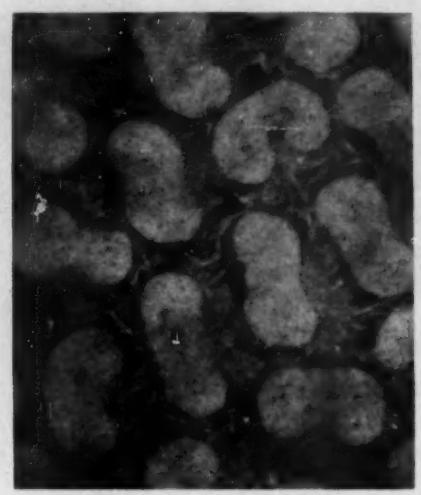


Fig. 5.—Flat preparation showing a complex system of lines running in the cytoplasm between nuclei. Rabbit; osmic acid fixation; polychrome methylene blue; × 950.

between and below the cells. It was found that aqueous methylene blue and toluidine blue stain produced a similar pattern but alcoholic methylene blue diffused rapidly through the cells without giving specific staining. When cornea, fixed in formal *saline*, was treated with 1% silver nitrate the basal "jig-saw puzzle" pattern could be recognized, but if the tissue was previously washed in formalin in *water* no silver staining occurred unless saline was again added, suggesting that the pattern was due to a precipitate of silver chloride and not to a specific argyrophilic substance within the cell. When an unstained fragment of well-fixed tissue was placed under a coverslip and polychrome methylene blue was added, no selective staining occurred as it gradually diffused into the tissue from the periphery of the fragment, again suggesting that the pattern seen when whole segments of cornea were stained was not due to an intracellular substance having special affinity for the polychrome stain.

In contrast to the tissue fixed in formalin, corneal endothelium which had been fixed in osmic acid took up the stain immediately, and in one preparation a complex system of pale lines could be seen running between the nuclei in the deeper part of the cell (Fig. 5). Some of these appeared to correspond to the dark pattern of lines which became apparent when the same stain was applied to formalin-fixed tissue.

It was very difficult to study cell structure in greater detail with the light microscope because of inadequate stain penetration into the formalin-fixed tissue. It was observed, however, that the cytoplasm in preparations stained with safranin or impregnated with silver contained numerous minute granules which in places seemed to coalesce to form a complex of tortuous fine lines of a much smaller order of magnitude than the "jig-saw" pattern revealed by the polychrome methylene blue stain. In some preparations the large pattern located beneath the nuclei of the cells and at the cell boundaries appeared to connect with the much finer pattern within the cell cytoplasm, but it was not possible to establish this definitely using the light microscope.

Electron Microscope.—The electron photomicrographs (Figs. 6 and 7) show a relatively thick osmic acid-positive layer, lining the anterior chamber surface of the cell. A relatively wide S-shaped intercellular space separates the cells and is broken up into compartments by adhesions between

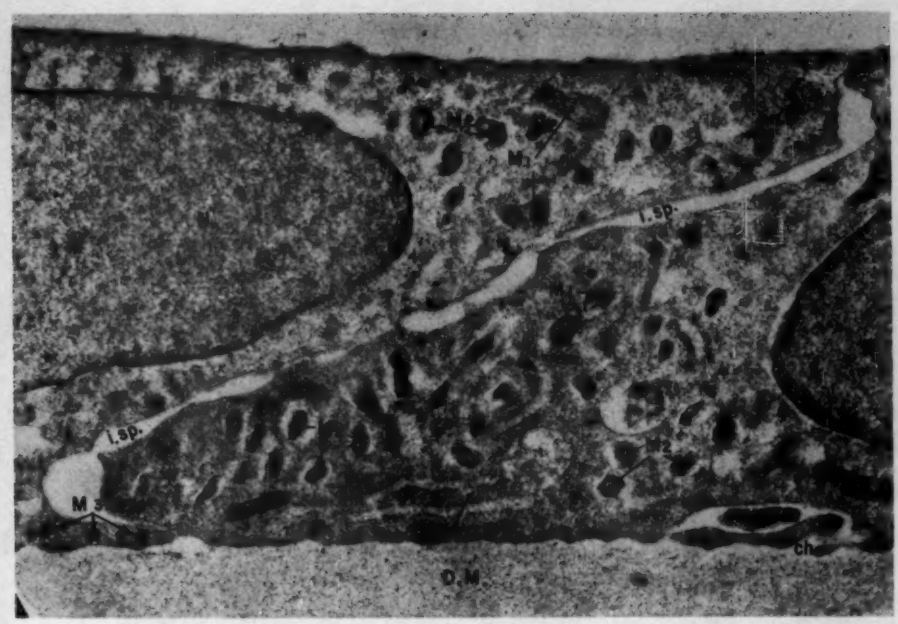
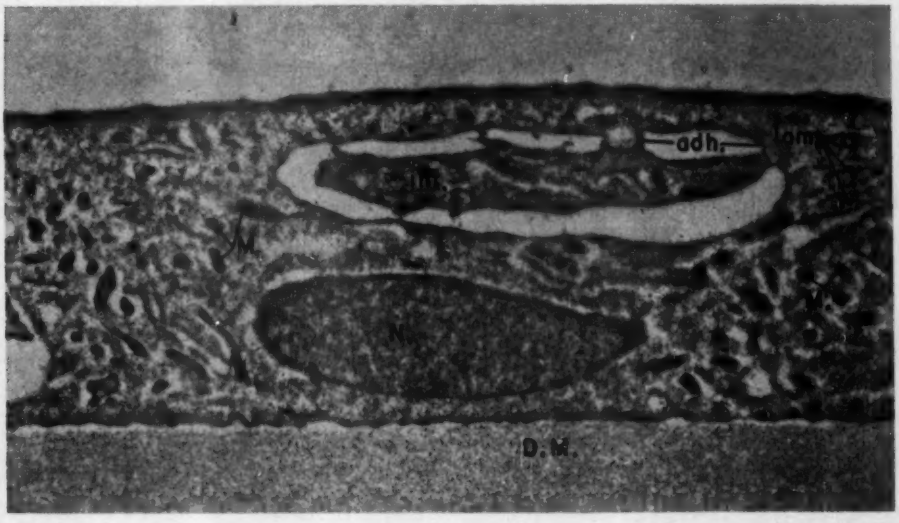


Fig. 6.—A wide osmic acid-positive surface layer; an intercellular space (*i.sp.*); paired mitochondria incompletely differentiated (*M1*), well differentiated (*M2*), degenerate (*M3*); cytoplasmic lamellae (*lam.*); potential channel (*ch.*) between cell and Descemet's membrane (*D.M.*). Rabbit. Reduced approximately ⅔ from mag. × 45,000.

Fig. 7.—An interdigitation (*int.*), adhesions between adjacent cell membranes (*adh.*), cytoplasmic lamellae (*lam.*) separated by double membranes, mitochondria (*M.*), nucleus (*N.*), Descemet's membrane (*D.M.*). Rabbit. Reduced ¼ from mag. × 20,000.



adjacent cell membranes, but there is no evidence for a special intercellular cement substance binding the cells together. Where the section passes obliquely through an interdigitation between cells, long processes of cytoplasm appear to extend from one cell into another. Several pictures show additional spaces lying between the deep surface of the cell and Descemet's membrane which unite with extensions of the intercellular space and appear also to connect with a complex channel system within the cell itself. The large nuclei do not show any special features, but the cytoplasm contains a variety of structures surrounded by a finely granular matrix. The most striking are numerous paired, darkly staining, ovoid structures containing a central thin cleft, which lie in a horizontal or vertical plane throughout the cells. These are undoubtedly mitochondria, and the fact that they are paired suggests that they form a C- or S-shaped cylindrical structure within the cell. The walls surrounding the central cleft consist of an outer and inner membrane, and when sectioned obliquely or longitudinally it is apparent that they are not homogeneous but are broken up by a complex system of fine channels. At one place a central cleft appears to bifurcate and communicate with the channel system within the wall. The ovoid paired structures vary considerably in size, and several of the smaller ones are undifferentiated round black smudges, probably representing a stage of degeneration.

Elsewhere in the cell the cytoplasm is separated into parallel lamellae by narrow lacunae or clefts which are lined by a conspicuous dark membrane. They resemble the layers of endoplasmic reticulum seen in other cells, but the characteristic spacing is lacking. In places the lacunae have a curved semicircular configuration, and some of them communicate with the intercellular space.

Comment

The staining behavior of corneal endothelium, rapidly fixed in formalin, towards many routine laboratory stains suggests that its surface membrane has unique permeability characteristics when comparison is made with lens epithelium and the endothelium of the adjacent trabecular meshwork. The surface of the corneal endothelium acts as a barrier to the penetration of many routine stains, but if the cells undergo vacuolation prior to fixation, the barrier becomes permeable. It would be of interest to determine whether these permeability characteristics are present in vivo and are related to the dense osmic acid-positive layer on the cell surface.

The staining found in the intercellular space and the complex "jig-saw puzzle" pattern lying between the cells and Descemet's membrane was originally thought to be a special intercellular cement substance or membrane. However, the fact that the pattern was revealed by several different stains which do not normally combine with the same structure led to the conclusion that the pattern was in reality due to the stains filling a complex network of spaces between and beneath the cells. This conclusion was strengthened by the observation that the pattern did not show up when tissue was stained under a coverslip (the spaces were presumably compressed) and also by the gaps which were present between cell membranes in the electron photomicrographs. There is no doubt that the width of these spaces has been exaggerated by shrinkage during fixation, and their precise size in vivo and the problem of whether or not they communicate with the anterior chamber by fine pores are questions which cannot be answered at present. It seems likely that the pattern of intracellular fibrils, described by Nuel and Cornil,[2] in stained osmic acid-fixed material is partly explained by the presence of these channels.

The ultrastructure of the corneal endothelium revealed by the electron microscope has not previously received any detailed consideration, although photographs of these cells have already appeared in the literature (Jakus[3]). Unusual findings ow-

ing to artifact are common when cells are examined under such high magnifications, and the extreme sensitivity of the corneal endothelium to injury makes it a particularly difficult tissue to study. For this reason great pains were taken to fix the endothelium rapidly with osmic acid, and, although slight shrinkage occurred, vacuolation did not develop and intracellular structures appear to be adequately preserved and imbedded.

Numerous C-shaped mitochondria are distributed throughout the cytoplasm, and the majority contain a central cleft running parallel to their long axis which is in contrast to the more usual transverse arrangement of the inner membranes, or cristae. In this respect they resemble some of the mitochondria seen by Holmberg[4] in the ciliary epithelium. The parallel double membranes within the cytoplasm appear related to the endoplasmic reticulum described by Palade,[5] but they do not demonstrate the characteristic spacing and are very limited in extent.

It is speculative to consider the functional role of the individual cell components, but many investigators believe that the corneal endothelial cells as a whole function as a pump, transferring fluid out of the cornea in order to maintain the stroma in a state of deturgescence. However, when comparison is made between the ultrastructure of the corneal endothelium and other fluid-secreting cells, such as the renal tubular epithelium, the ciliary epithelium, and the choroidal plexus, all of which possess elaborate infoldings of cell membranes (Pease[6]), there are few points of similarity; on the basis of morphology one would not expect the endothelium to have a similar function. The staining behavior suggests, on the contrary, that the endothelium may act as a barrier between the anterior chamber and corneal stroma and that the extensive system of potential channels around and within the cell may permit essential nutrients to reach the cell which do not diffuse rapidly enough from the anterior chamber. There was no evidence of a communication between the anterior chamber and any of the intracytoplasmic structures through the relatively thick osmic acid-positive layer on the cell surface, comparable to that seen in the limiting membranes of vascular endothelium. No intracellular vacuoles were seen which might suggest a process of pinocytosis, nor was there any infolding of the plasma membranes which is so characteristic of fluid-secreting cells.

Summary

A study of corneal endothelium rapidly fixed in formalin has shown that many routine stains fail to penetrate the intact cell membrane, although they fill a tortuous system of channels in the intercellular space between the cells and Descemet's membrane.

Electron photomicrographs confirm the presence of extensive potential channels around the cells and demonstrate in the cytoplasm a complex arrangement of C-shaped mitochondria and elements of the endoplasmic reticulum. The absence of vacuoles and infolded cell membranes suggests that the corneal endothelium is not involved in active water transport.

This investigation was conducted in the Department of Pathology of the Institute of Ophthalmology in London, England, while the author held a Wernher Pigott Medical Research Council Fellowship. Prof. Norman Ashton and Dr. David Maurice offered many suggestions. Dr. Friedman, of the Institute of Otolaryngology, prepared the electron photomicrographs.

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REFERENCES

1. Speakman, J. S.: Endothelial Cell Vacuolation in the Cornea, Brit. J. Ophth. 43:139-146, 1959.

2. Nuel, J. P., and Cornil, F.: De l'Endothélium de la chambre antérieure de l'œil, particulièrement de celui de la cornée, Arch. opht. 10:309-325, 1890.

3. Jakus, M. A.: Studies on the Cornea: 1. The Fine Structure of the Rat Cornea, Am. J. Ophth. 38:40-53 (July, Pt. 2) 1954.

4. Holmberg, A.: Ultrastructural Changes in the Ciliary Epithelium Following Inhibition of Secretion of Aqueous Humour in the Rabbit Eye,

Monograph, Södertälje, Axlings Bok and Tidskriftstryckeri, 1957.

5. Palade, G. E.: The Endoplasmic Reticulum, J. Biophys. & Biochem. Cytol. 2:85-98 (No. 4, Pt. 2) 1956.

6. Pease, D. C.: Infolded Basal Plasma Membranes Found in Epithelia Noted for Their Water Transport, J. Biophys. & Biochem. Cytol. 2:203-208 (No. 4, Pt. 2) 1956.

Bilateral Melanoma of the Choroid Associated with Leukemia and Meningioma

HERBERT WIESINGER, M.D.; G. W. PHIPPS, M.D., and DuPONT GUERRY III, M.D., Richmond, Va.

The bilateral occurrence of a malignant melanoma of the uveal tract is of sufficient rarity to warrant a short report. Schies-Gemuseus [1] has reported such a case as did Landsburg.[2] Carter [3] reported bilateral malignant melanomata of the irides. Similar cases were seen by Dixon [4] and Hirschberg.[5] However, in all these cases the tumor in the fellow eye was not proven histologically. The first proven bilateral case was that of Shine [6] in which the choroid and iris were involved respectively; Cordes and Cook [7] reported a similar case with histological proof. A. B. Reese,[8] in his book, mentions having seen one such case of bilateral melanomata of the uveal tract. In Landsburg's case, the melanomata occurred simultaneously. In Dixon's case, the interval was six months; in Hirschberg's case, one year; and in Shine's case, three years. Cordes and Cook's case was interesting in that, in addition to the malignant melanoma, a nevus of the lower lid of one eye was present.

Ten Doesschate [9] reported a case of a melanoma of the choroid where, immediately after enucleation, a melanoma occurred in the choroid of the other eye. He interprets this as a metastasis of the previous tumor. There were multiple metastases elsewhere and melanuria in this case. Specimens from the skin and both eyes showed the tumor to be composed of the same type cells.

Submitted for publication June 29, 1959.

From the Department of Ophthalmology, and the Hunton Memorial Eye Bank of the Medical College of Virginia.

Report of Case

A 32-year-old white woman was first admitted to the Medical College of Virginia

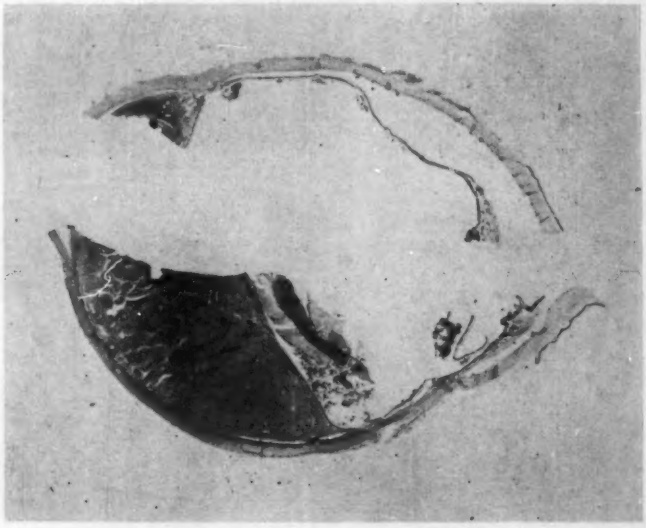

Fig. 1.—Left eye (enucleated, 1948).

in May, 1954, at which time she gave birth to her fifth child. The birth was uneventful. At the time, the medical history included the removal of the left eye at another hospital because of a tumor six years before at the age of 26. The tumor had been found to be a mixed cell type of melanoma of the choroid. The block of the specimen was sent to us, and the pathological findings will be discussed later. The only other interesting point was a family history of leukemia, which was responsible for the death of one sister.

She was next seen in October, 1955, with the complaint of blurred and distorted vision in the remaining eye of one week's duration. Examination at that time revealed a solid detachment of the retina in the posterior segment of the right eye nasal to and partially overhanging the disc. Transillumination was positive and in view of the grayish-green color of the retina, a diagnosis of melanoma of the choroid was made. She was admitted to the hospital and studied for evidence of metastases. Such studies were found to be negative, but a white blood count of 36,000 was found on hematological survey. Further investigation of the hematologic picture revealed the presence of a characteristic stem cell leukemia, and the idea of enucleating the remaining eye was abandoned. The patient was started on 6 mercaptopurine with a rapid improvement in her general condition. The white blood count at discharge was 5,700. She was followed at regular intervals thereafter and maintained her weight and general fair health until her terminal admission in September, 1956. Prior to this, the 6 mercaptopurine had been stopped for six weeks. In August, 1956, the white count rose from 3,750 to 99,000, and a generalized lymphadenopathy, splenomegaly, and ulcerating lesions in the mouth were noted.

Eye examination revealed the size of the tumor to be greatly increased, and by then the nasal one-third of the retina was involved with bulging far into the vitreous, the disc being obscured almost entirely. During hospitalization the 6 mercaptopurine was increased. Blood cultures were positive for pseudomonas. The white count fluctuated between 50,000 and 60,000 with 17,000 platelets and a hemoglobin of 8. She developed nausea, vomiting, hemorrhagic spots on the trunk and extremities, a spiking temperature of 104 F, and died a respiratory death 16 days after admission. At autopsy, leukemic splenomegaly, hepato-

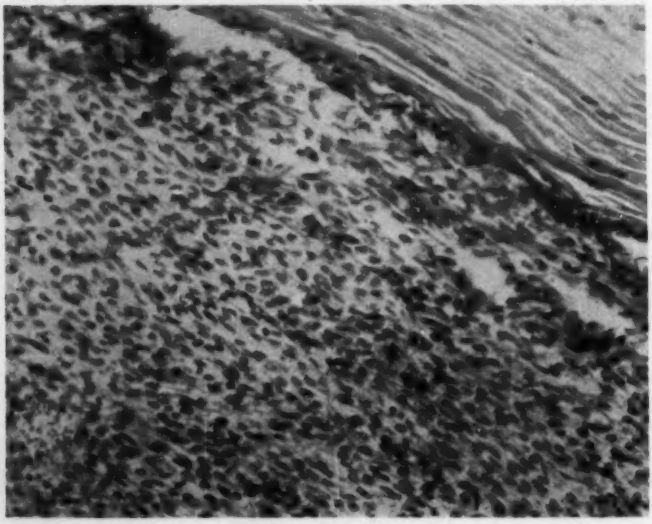

Fig. 2.—Higher magnification of tumor—left eye.

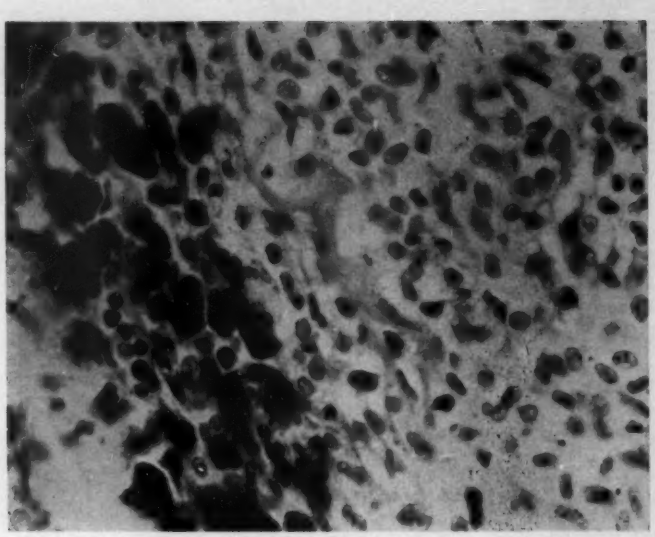

Fig. 3.—High-power magnification of tumor—left eye.

megaly, and lymphadenopathy were found. There was also leukemic infiltration surrounding the adrenals, kidneys, and the retroperitoneum. No evidence of metastasis from melanoma was found. Another interesting finding was that of a sharply circumscribed and outlined ovoid mass at the base of the left frontal lobe originating from the meninges which proved histologically to be a fibrous meningioma. No distortion of the cerebral ventricles was noted.

Ocular Pathology

The following is an excerpt of the gross description of the left eye which was enucleated in 1948, by Dr. Moran.

"The external portion of the eyeball is entirely normal. A portion of normal optic nerve measuring 0.3 cm. protrudes from the posterior surface. The cornea and lens are normal. The anterior chamber is filled with normal fluid. The posterior chamber is entirely filled with a blood clot and a large cystic mass. The mass fills the entire chamber and its exact origin cannot be determined. Its cut surface is flat, smooth, and yellowish-gray around the peripheral portion. The central portion, however, is bloody. Numerous bluish-black pigmented areas are seen on the cut surface and, in some areas, the nodule is almost solidly black."

Microscopic sectioning revealed a primary malignant new growth made up of moderate sized or large spindle shaped, round or polyhedral cells arranged in large sheets almost entirely without a fibrous tissue stroma. In some areas, a fasciculated appearance is noted. The nuclei vary in appearance. Most of the nuclei are large, pale and ovoid with a definite nucleus. Many nuclei are large, irregular, and hyperchromatic. Moderate pigment deposition is noted throughout the tumor. Numerous large blood vessels apparently lined by tumor cells are scattered throughout.

The right eye, which was enucleated at autopsy in 1956, presented no unusual features grossly. Microscopic examination was as follows:

The anterior chamber, iris, and lens are normal. Immediately overlying the optic nerve, there is a large retinal detachment involving about 60% of the retina. Beneath this is a pale, moderately pigmented tumor about 1 cm. in diameter and having an altitude of 0.8 cm. No evidence of extension of the tumor in the scleral sections

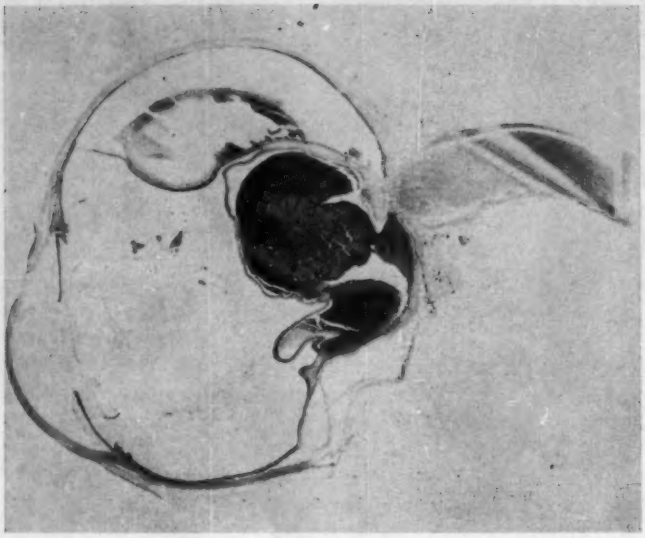

Fig. 4.—Right eye (enucleated at autopsy, 1956).

is seen. The choroid is heavily pigmented. Posteriorly there is a tumor arising from the choroid which is composed largely of spindle cell B type cells with very little pigmentation and fibrous stroma, except in a spotty distribution. There are some hemorrhages into the tumor and there is also a large amount of partially coagulated blood and some proteinous fluid between the choroid and retina. At the apex of the dome of the tumor there is a chorioretinal adhesion. The retina is normal. The optic nerve does show a few clumps of melanoma cells posterior to the lamina cribrosa, some of which are pigmented and some of which are amelanotic, but no tumor cells are noted at a distance of more than 2 mm. from the lamina cribrosa.

Fig. 5.—Higher magnification of tumor originating adjacent to optic nerve.

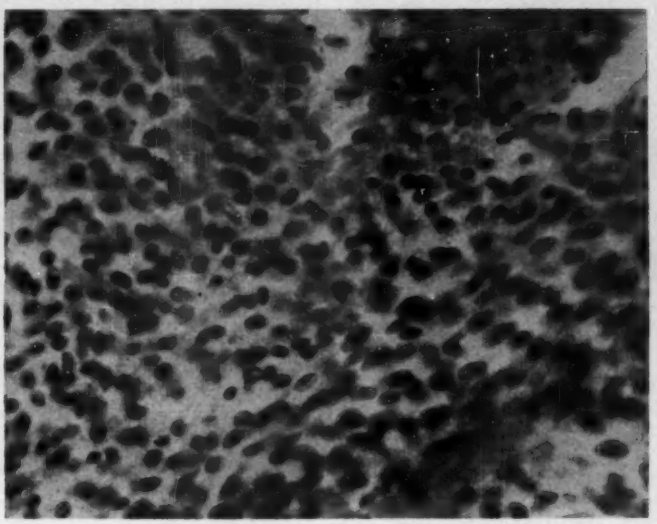

Fig. 6.—High-power magnification of cell structure of tumor in right eye.

Summary

A case of "primary" bilateral melanoma of the choroid is presented. The interval between the appearance of the tumors was seven years. No evidence of metastasis was found either clinically or on autopsy. It is interesting that this patient also suffered from a stem cell leukemia, which was responsible for her death, and a fibrous meningioma of the base of the skull.

2015 Monument Ave. (20).

REFERENCES

1. Schies-Gemuseus, H.: Klein-Zelliges Melanosarcoma choroidis beider Augen, Arch. path. Anat. 33:495, 1865.

2. Landsburg, M.: Sarcoma der Chorioidea Sehr langsamer, eigentuemlicher Verlauf, Arch. Opht. 15:210, 1869.

3. Carter, R. B.: Case of Sarcomata of Both Irides, Tr. Clin. Soc. London 7:60, 1874.

4. Dixon, L.: Cases of Sarcoma of Choroid and Retinitis Albuminurica, Tr. Am. Ophth. Soc. 2:432, 1878.

5. Hirschberg, J.: The Malignant Tumors of the Eye: II. Sarcoma Uveae, Arch. Ophth. 10:71, 1887.

6. Shine, F. W.: Report of a Case of Bilateral Sarcoma of the Uveal Tract, New York Eye and Ear Inf. Clin. Rep. 1:31, 1930.

7. Cordes, F. C. and Cook, R. D.: Simultaneous Bilateral Primary Ocular Malignant Melanoma, Tr. Am. Ophth. Soc. 47:80, 1949.

8. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1951, p. 222.

9. Ten Doesschate: Over metastatisch Sarkoom in het ogg, Nederl. tijdschr. v. geneesk. 2:1432, 1919.

Case Reports

Aneurysm of the Anterior Cerebral Artery

Perimetric Findings as the Only Presenting Neurological Sign

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This case is of interest because of the unusual location of an aneurysm, its effect on the optic nerve preoperatively, and the method of eliciting perimetric findings.

Report of Case

On Feb. 27, 1958, a well-developed Caucasian man was first seen with the following symptoms:

1. Almost continuous headache over the left eye for one year, increasing in severity for the past two months.
2. Pressure sensation behind the left eye, aggravated by cough.
3. Blurred vision after cough.
4. Pain over left eye on sneezing.

The entire ocular examination was negative except for the perimetric findings. The tangent screen test and 3/1,000 white office light revealed a left nasal contraction in the upper quadrant.

With a history of headache and a field finding, the patient was referred to a neurological department for study. He was sent back with a negative finding and for observation. I immediately performed the test under the same condition and to my dismay could not obtain the nasal defect. A few more visits followed only to find full fields.

On Sept. 15, seven months later, in a somewhat discouraged mood, the patient volunteered the information that his headache increased upon bending forward. He was instructed to bend head down and remain so for 15 minutes. A repeat field test revealed the same original nasal defect. A return trip to the neurological department, where an arteriogram was made, revealed an aneurysm of the left anterior cerebral artery.

On Sept. 25, operation was performed. The aneurysm was treated successfully by slowly applying a clip. Except for a postoperative convulsive seizure, the patient was symptomless.

On Nov. 29, 1958, his vision was blurred. Visual acuity was taken and found to be finger counting at 8 ft.; the disc was pale and has remained so up to the time of this report.

On Dec. 15, fearing failure of the metal clip to compress the aneurysm, a repeat arteriogram was taken, but no filling defect was seen. Otherwise the man is well, and working at the present time.

160 Summer St.

Submitted for publication June 29, 1959.

Annual Reviews

Neuro-Ophthalmology

JOHN WOODWORTH HENDERSON, M.D., Ann Arbor

In approaching the assignment of selecting the pertinent neuro-ophthalmologic literature for the past year, the reviewer feels much like a guest at a "super-smorgasbord." Selection is necessarily influenced by the interests of the reviewer, and omission of certain material has doubtless resulted. There is reduplication of material from other reviews, especially that of Hollenhorst in the May, 1959, issue of the A. M. A. Archives of Ophthalmology,[1] and for further material on optic nerve the reader is referred to his report.

Papilledema

The only generally accepted pathogenesis of papilledema is compression of the central retinal vein in its sheath, according to Leinfelder.[2] This, however, does not explain identical swelling in other conditions where increased intracranial pressure is not causative. Recent anatomic studies have confirmed that the capillaries of the nerve head are derived from the circular choroidal artery of Zinn. Congestion and stasis in these capillaries are the primary cause of edema of the nerve head, and papilledema from any cause will have the same appearance. Since these disc vessels are independent of the retinal circulation, the retina does not take part in such edema.

The experimental production of papilledema was a failure in dogs, but successful in monkeys in a study reported by Glew et al.[3] In two of six monkeys, bilateral papilledema was elicited by inflation of a subdural balloon over the temporal lobe. The papilledema took about two weeks to develop, and two or three weeks to subside, similar to that of intracranial lesions in man. It could not be explained why a negative result was present in the other monkeys, since the recorded intracranial pressure was fully as elevated.

The fear of lumbar puncture in patients with increased intracranial pressure is allayed by Korein and associates.[4] They report on 129 patients with elevated cerebrospinal fluid pressure, 70 of whom had papilledema. The use of careful diagnostic lumbar puncture may prevent unnecessary ventriculography or surgery, and the chance of complication in the presence of papilledema is less than 1.2%.

The differential diagnosis of an elevated disc may be extremely difficult in some cases. Huber and Cagianut[5] review the differences in morphology, visual fields, and associated retinal findings to distinguish between papilledema of malignant hypertension and true choked disc. Chamlin[6] points out that in unilateral papillitis floaters or flare in the aqueous point to inflammation rather than to papilledema. He states that these are visualized more adequately after wide mydriasis with 10% neosynephrine, but one wonders whether release of pigment granules from the iris in certain cases might not confuse the issue.

Papilledema can be caused by a variety of conditions. It may be due to iron deficiency anemia as noted by Lubeck,[7] since iron therapy caused its prompt disappearance. It can be one of the symptoms of chronic vitamin A intoxication. Oliver and Havener[8] believe that there may be increased cerebrospinal fluid secretion, headaches, and extraocular palsies, as well as papilledema. The polycythemia associ-

Received for publication July 13, 1959.

ated with subtentorial vascular tumors may elicit papilledema, especially if the hemoglobin values are greater than 18 gm. %. Starr et al.[9] noted the difficulty in differential diagnosis between the neurological complications of polycythemia vera and posterior fossa lesions. Phlebotomy gives relief of symptoms in polycythemia vera and subsidence in papilledema, but no help is gained in cerebellar vascular tumors. It is noted that recurrent papilledema and subarachnoid bleeding may result from an infarcted spinal neurofibroma by Halpern and associates.[10] The cerebral symptoms are preceded by spinal pain, and the papilledema may result from elevated cerebrospinal fluid protein levels with diminished absorption of the fluid.

Further evidence of the infrequency of the Foster Kennedy syndrome is provided by Lasco et al.,[11] who found 40 instances in 2,272 cases. Only 30 were due to intracranial tumors, and the multiplicity of etiologies is stressed, including 7 cases due to ocular disease. Bynke[12] found only 17 instances of the syndrome in 1,400 cases with expanding intracranial lesions. The most frequent cause was sphenoid wing meningioma (11 cases), and only one instance was found in 180 patients with frontal lobe tumors.

Optic Nerve

Visible abnormalities of the optic nerve head may be associated with visual field defects. Petersen[13] reports on nine cases of optic nerve pits; six patients had associated paracentral scotoma originating at the blind spot, or an arcuate scotoma leading from the blind spot to a large nasal quadrant defect. A thorough review of drusen of the papilla by Francois and Verriest[14] points out that drusen can be associated with acquired disease of the optic nerve or globe, may be secondary to another heredodegenerative affection, or may be idiopathic. The latter are rarely visible before puberty; they cause visual disturbance in the form of visual field defects such as enlargement of the blind spot and nerve fiber bundle scotomas.

Igersheimer[15] notes that lesions of the nutritive vessels of the optic nerve may produce visual loss. He also discusses intracanalicular edema of the optic nerve as a cause of acute loss of vision. Such an entity of acute edematous intracanalicular optic neuritis is postulated by Klíma et al.[16] in a patient where decompression of the optic canal resulted in visual recovery. They believe that the majority of cases of opticochiasmatic arachnoiditis are really instances of primary optic neuritis with a secondary reaction in the arachnoid.

The differential diagnosis of optic nerve lesions is difficult in many cases. If the disc is not elevated, one must consider retrobulbar neuritis, macular disease, and intracranial expanding lesions, according to Carroll.[17] In reviewing 135 patients with retrobulbar neuritis, Rosselet[18] found five cases with cerebral tumor involving the intracranial optic nerve. In almost one-third of the patients no cause was found. The perplexing problem of bilateral retrobulbar optic neuritis is reported by Hierons and Lyle[19] in a group of 47 observed cases. In adults they found a number of patients with almost simultaneous rapid loss to maximum in less than one week. Improvement or recovery occurred in one-half the cases, and in none were there symptoms or signs of multiple sclerosis. In contrast, in the group where an interval of several months to years occurred between the two eyes, almost 75% recovery was noted, and 40% of the patients had associated neurological signs. In 13 children in the series, good recovery resulted, and only one had signs of multiple sclerosis. The authors believe that a localized form of encephalomyelitis is responsible for the cases in childhood.

The relationship of optic neuritis to systemic disease continues to be of interest. Hamilton, Ellis, and Sheets[20] review 28 cases with pernicious anemia and optic neuropathy and add a patient of their own.

The retrobulbar neuritis was cured by vitamin (B_{12}) administration. They recommend the use of the Shilling test of gastrointestinal absorption of cobalt^{60}-labeled vitamin B_{12} in establishing the diagnosis of pernicious anemia in a patient with an optic nerve lesion of obscure etiology. A higher absorption than normal proves the absence of intrinsic factor. Fourteen patients with uncontrolled diabetes mellitus and optic neuritis are reported by Skillern and Lockhart.[21] In twelve, a recent visual loss led to the discovery of moderate to severe diabetes, and although control of the disease arrested the visual loss in all but one case, only one patient showed any significant visual improvement.

Scattered reports of viral etiology in optic neuritis continue to appear. Sasso[22] observed papillitis occurring 10 days after varicella in a child. The dense central scotoma disappeared on treatment. Eleven cases of retrobulbar neuritis without other signs were studied by De Vincentiis[23] by multiple laboratory tests, but no specific virus was implicated.

Lactation neuritis has lost favor in recent years. Kepes and Remanár[24] report a case of disseminated encephalitis which began with symptoms of a lactation neuritis of the optic nerve. They suggest caution in making the diagnosis, since in the absence of neurological signs there is no difference between so-called lactation neuritis and the acute neuritis of multiple sclerosis. Mistaken diagnosis of optic neuritis due to intracranial tumor may result in cases with unilateral optic nerve compression by a deeply situated mucocele of the sphenoid or posterior ethmoid sinuses. Petit-Dutaillis et al.[25] noted that rhinologic examination is often negative, but that a history of sinusitis, x-ray changes, and paroxysmal occipital, and vertex headaches aids in the diagnosis.

Wagener[26] recommends transfrontal craniotomy as the best approach to gliomas of the anterior visual pathways. It allows more chance for complete removal of the tumor. Most such tumors are low-grade astrocytomas, and the prognosis is good if the tumor does not involve the chiasm. Forty-six pathologically proven cases of primary glioma of the optic nerve, chiasm, or tract observed during a 41-year period are reported by Dodge et al.[27] of the Mayo Clinic. Only 12 of the lesions were limited to the optic nerve and 34 were in the chiasm or optic tract. Thirty-three were found in children. Proptosis was the major finding with glioma of the optic nerve, and bilateral visual loss occurred in those with chiasmal or tract origin. All types had a tendency to spread toward the brain, and only rarely into the orbit; hence orbital exenteration is rarely indicated.

Metastatic disease of the optic nerve is rare. Weizenblatt[28] adds five cases to the literature, all being carcinomata. A further personal case of metastatic melanoma involving the intracranial optic nerves is noted. She feels that the initial lesion to the intracranial optic nerve is in the sheaths, which are rich in blood vessels. Norton[29] documents a case of breast adenocarcinoma with isolated distal optic nerve metastasis and no other intracranial involvement. The sudden occurrence of unilateral visual loss in an otherwise apparently healthy person may be the first sign of localization of intracranial metastatic disease. Lasco, Nicoleso, and Niculiu[30] report two such cases where visual involvement preceded other general clinical signs.

A new form of optic neuritis is reported by Reese and Carroll,[31] who present 17 cases with papillitis occurring from 6 to 12 weeks after cataract surgery. A drop from normal postoperative vision to a range from 20/70 to 20/200 results from the associated central scotoma. The vision returned to 20/30 or better in only six patients, and there was ultimately some pallor of the nerve and visible atresia or sclerosis in one or more of the smaller arterioles about the disc. The cause is probably vascular, and since there is a possibility of cranial arteritis, steroid treatment is suggested.

The necessity of explaining optic atrophy is documented by Rougier and Royer,[32] who recommend cerebral angiography, having discovered anterior cerebral arterial aneurysm in one patient, and a meningioma of the tuberculum sella in another. Confusion may be engendered by atypical field defects in association with hereditary optic atrophy. Manchester and Calhoun[33] report a family with dominant atrophy where the first patient who had a bitemporal field defect was spared intracranial exploration by the discovery of a similar difficulty in others of the kinship.

Blood Supply to Visual System

The knowledge of blood supply to the visual pathways has been furthered by Dawson,[34] who studied the chiasmal circulation in 230 specimens. The prechiasmal arterial anastomosis supplies the surface arterial plexus on the intracranial portions of the optic nerves and chiasm. This anastomosis occupies the angle between the optic nerves and consists of a series of irregular arterial loops fed by prechiasmal branches of the ophthalmic artery, superior chiasmal arteries from the anterior cerebral, and inferior chiasmal arteries from the internal carotid.

Variations in the circle of Willis have been noted frequently in the literature on arteriography. Alpers et al.[35] analyzed the circle in a selected series of 350 normal brains. They found a normal configuration of the polygon in 52.3%. A truly incomplete circle was found in only two specimens; in both, the left posterior communicating artery was absent. The most frequent anomaly was a filiform caliber of the component vessels, most often in the posterior communicating arteries; duplication of vessels was present in 18.9%, and multiple anomalies were found in 13.4%.

The blood supply of the optic nerve is such that in a significant number of cases circulatory disturbances affecting the distal portion of the nerve produce an inferior hemianopsia. Piper and Unger[36] report that the predominance of inferior field or superior optic nerve lesions may be due to the fact that the anterior branch of the central artery of the optic nerve terminates in the upper portion of the nerve above the axially located central retinal artery.

The contention that the ratio of nerve cells in the lateral geniculate nucleus and of fibers in the optic nerve is 1:1 is supported by Sullivan et al.[37] By a special counting technique they reached a final figure of just over 1,000,000 cells—close to the number of optic nerve fibers reported by earlier workers.

Vascular Diseases Affecting the Visual System

Interest continues apace in the general problem of major cerebral vascular occlusive disease. Pickering[38] recalls that as early as 1913 Ramsay Hunt drew attention to the possible importance of abnormalities of the carotid artery in causing lesions of the brain, noting that visual disturbances and vascular changes in the optic nerve may precede other organic cerebral symptoms. Pickering reports two cases with unilateral, almost complete blindness, at first episodic but soon permanent. Both had no other cerebral signs, and clots were removed from atheromatous internal carotid arteries. In each, the original diagnosis was that of occlusion of the central retinal artery, although the angiograms showed patent ophthalmic arteries. He emphasizes that one must consider the possibility of a more remote arterial lesion when making the diagnosis of central retinal artery occlusion.

The ophthalmologist attempting to keep pace with the increasing literature on vascular occlusion will be aided by the "Classification and Outline of Cerebrovascular Diseases," published by the National Institute of Neurological Diseases and Blindness.[39] It supplies a working outline of proper diagnosis. Further basic material is presented by Hollenhorst,[40] who reported on the ocular manifestations of 124 patients, who had insufficiency or thrombosis of the carotid artery system. The major

symptom of intermittent insufficiency was amaurosis partialis fugax, cured in most instances by anticoagulant therapy. Other ocular manifestations of carotid disease included retinopathy on the side of the affected carotid artery, asymmetric hypertensive retinal vascular changes; and lowering of pressure in the retinal artery on the side of the affected carotid artery in 83 patients. He stressed the importance of establishing the diagnosis of carotid occlusive disease during the period of intermittent insufficiency.

There were many reports on ophthalmodynamometry in the diagnosis of these patients during the past year. Hollenhorst [41] states normal values to be 70-80 mm. Hg. systolic and 30-35 mm. Hg. diastolic. A difference of more than 10 mm. Hg. in the pressure readings of the two retinal arteries indicates diminished or absent blood flow in the carotid artery on the side of the lower pressure. Mones [42] believes that the absolute pressure value of the reading is of no significance, and that the only important element is the comparative values between the eyes of one patient, or in comparing values in one eye before and after surgical manipulation of the ipsilateral carotid. He notes that about 80% of patients with carotid occlusive disease show a significant lowering of pressure on the ipsilateral side. Van Allen, Blodi, and Brintnall [43] used ophthalmodynamometry in three cases of proven internal carotid occlusion. The pressures on the occluded side were lower by 30%-49% systolic and 25%-54% diastolic. Two of the three patients were operated upon without preliminary angiography on the basis of retinal arterial pressure differences. Fifty normal subjects were found to have reproducible retinal artery measurements by Spalter.[44] He found significant pressure differences ranging from 29%-86% lower on the occluded side in 9 of 10 patients with known carotid artery thrombosis. Collateral had probably developed in the tenth patient who was examined three years after occlusion. Two other patients had occlusion distal to the origin of the ophthalmic artery, and in one the retinal artery pressures were higher on the occluded side. He believes that in intermittent amaurosis the systemic blood pressure falls transiently below the available collateral via the external carotid. In a detailed monograph, Belmonte-Gonzales [45] reports a study of 1,181 cases. He advises that the ophthalmodynamometer first be used in a series of normal cases before relying on conclusions from its use. Mueller [46] concludes that the measurements obtained are of the pressures half-way between the origin of the central retinal artery and the artery at the disc. He notes that alterations in the measurements will occur in cases of venous engorgement, and recommends the use of the ophthalmodynamometer in evaluation of drugs acting on the cerebral vascular system. Some of the disadvantages of the instrument are eliminated by a new ophthalmodynamometer constructed by Schirmer.[47]

Another clinical aid in the diagnosis of carotid artery insufficiency is a murmur heard usually over the carotid bulb. According to Crevasse and Logue,[48] a localized systolic murmur may be the first sign of carotid insufficiency. As the lumen narrows further, and if collateral circulation is inadequate, a continuous murmur will appear. They suggest carotid auscultation in patients in whom the diagnosis of cerebral thrombosis has been entertained. Absolute diagnosis by arteriography can be made safely with only 2 cc. of Hypaque (diatrizoate sodium), Oldendorf [49] reports. The method visualizes only the carotid system and minimizes trauma.

Occlusion of the basilar artery also produces ocular signs. Carvioto et al.[50] studied 14 cases proved at autopsy. Most of the patients were elderly males. A

picture of headache, dizziness, vomiting, vertigo, visual disturbances, and dysarthria rapidly evolving to anarthria was observed, usually followed by coma. Abnormal eye movements in eight patients included disconjugate gaze and nystagmus. Fixation of the eyes in the midline, with negative response to caloric stimulation, anisocoria, miosis, impaired corneal reflexes, and facial palsy were also noted.

The value of anticoagulant therapy in these patients is demonstrated by Millikan and his co-workers.[51] In a study of 317 patients thus treated, 94 were classified as having intermittent insufficiency in the vertebral-basilar system, and in 90 of these the attacks stopped completely soon after the anticoagulant effect of the drugs was demonstrated by laboratory tests. A group of 85 patients with intermittent insufficiency in the carotid system was treated, and in 82 the characteristic attacks ceased. Incidence of hemiplegia in advanced carotid thrombosis is remarkably less than in untreated cases.

Continued interest in temporal arteritis is evidenced by two major articles. Wagener and Hollenhorst[52] note that 54 of 122 patients with temporal arteritis observed at the Mayo Clinic had some degree of visual impairment. Fifteen were blind in both eyes, 18 in one eye. Diagnosis in most cases could be made from the history, palpation of the temporal and occipital arteries, and an accelerated sedimentation rate. Occasional biopsy of the involved artery was necessary. Early diagnosis and treatment with steroids reduces the incidence of blindness and simultaneous anticoagulant therapy is probably of help. Fifty consecutive patients with temporal arteritis are reported by Parsons-Smith[53] who states that corticotropin (ACTH) given the same day as the onset of blindness restores the sight in every eye so treated. He recommends that all occlusive incidents in blood supply to the retina or optic nerve in elderly people who have no other evidence of ocular disease be treated with a course of corticotropin.

The possibility that cerebral venous thrombosis may have ocular signs is noted by Krayenbühl.[54] One patient with venous thrombosis of the left occipitoparietal area had visual reduction to light perception with right-sided motor signs; complete recovery followed treatment. A second patient showed papilledema as a result of massive right cortical thrombosis. Both followed systemic infections, and angiography was essential to diagnosis.

Intracranial Aneurysms

The association of coarctation of the aorta with cerebral arterial aneurysms is confirmed by Tyler and Clark,[55] who found three proved and two probable aneurysms in a series of 200 patients with coarctation. Savin[56] notes the association of ophthalmoplegic migraine with aneurysms of the internal carotid or posterior communicating arteries. Eight cases of sellar aneurysms are presented by Rhonheimer,[57] who found the essential symptom to be a more or less sudden, successive development of an incongruous chiasmal syndrome with unilateral, often paroxysmal headaches. Occasional ocular muscle paresis, trigeminal involvement, and slight sellar enlargement with typical calcifications are present. He reports generally negative arteriographic findings in this series. Troupp et al.[58] find that not one of six patients with an internal carotid aneurysm causing oculomotor palsy has recovered completely. All were assumed to have direct nerve compression. In other cases where oculomotor palsy was due to subarachnoid hemorrhage rather than direct pressure, recovery was excellent. Medial rectus and levator palsy recovered much better than superior rectus and inferior oblique involvement.

The ocular signs of spontaneous meningeal hemorrhage are stated to be ocular palsies, papilledema, retinal hemorrhages, and visual

field changes by Paufique et al.[59] Extraocular palsies occur in from 20% to 60% of cases with aneurysms of the circle of Willis. Papilledema and retinal hemorrhages occur in about 10% of cases but are of serious prognostic import. The rare occurrence of massive vitreous hemorrhage in association with carotid aneurysm and subarachnoid bleeding is reported by Rougier et al.[60] This finding can lead to confusion in diagnosis, as in a patient seen by the editor where a severe uveitis was first suspected.

The ocular findings in 17 cases of carotid-cavernous fistula are reviewed by Henderson and Schneider.[61] Impairment of vision was the most frequent entering complaint, with diplopia and headache next. Findings were proptosis, retinal and conjunctival venous congestion, and an audible bruit. Objective visual loss was found in over half the patients, and ocular muscle palsy, more often abducens, occurred in over 50%. Secondary glaucoma was either early, based on venous congestion, or late in association with blindness and cataract formation. Combined cervical and intracranial internal carotid ligation with clipping of the ophthalmic artery reduces the proptosis and other signs, and is recommended where possible. In contrast, Esteban Aranguez and Gallego Tejedor[62] report only partial reduction of exophthalmos after simple carotid ligation. Thiel[63] in reviewing the ocular complications of intracranial aneurysms notes that in obscure cases auscultation of the head and arteriography are essential. Pulsating exophthalmos may not necessarily always be due to carotid-cavernous fistula. Calmettes et al.[64] report an unusual case where head injury led to pulsating exophthalmos in a patient with cranial osseous metastases of a thyroid neoplasm. Radioiodine treatment produced recovery from the ocular signs.

Enoksson and Bynke[65] state that the usual visual field defect of racemose arteriovenous aneurysms of the brain is a homonymous hemianopsia. The optic radiation may be injured by direct compression or by cerebral ischemia as a result of the vascular shunt. Intracranial bleeding may also cause compression. Migraine may be the only symptom of a posteriorly located arteriovenous aneurysm.

Cerebral Tumors

Several papers have dealt with the findings in brain tumors in children. Walsh[66] notes that the chronic development of multiple cranial nerve palsies in children is always due to neoplasm. One might expect a delay in the onset of papilledema because of suture separation, but papilledema is an early finding in many cases, probably related to the higher incidence of fourth ventricle involvement. Seventy-four per cent of a series of 172 verified brain tumors in children were discovered to be papilledema, according to Carbajal.[67] Other evidences of increased intracranial pressure were suture separation and dilatation of one or more ventricles, the latter being the most reliable sign. Matson[68] points out that there are a number of tumors in children which have a fairly good outlook. These include cerebellar astrocytoma and craniopharyngioma. Total excision is possible in many of these patients.

Tumors of the chiasmal region continue to draw considerable attention. Heimbach[69] reports 105 cases of verified pituitary adenomata after treatment by transfrontal craniotomy and x-ray irradiation. The indication for operation was rapid visual deterioration. Classic bitemporal hemianopsia was present in 59%, monocular field involvement was noted in 10 patients, and homonymous hemianopsia in six. Complete visual recovery ensued in 27.6%, marked improvement in 28.6%. He believes that the degree of disc pallor is of no help in estimating prognosis, although complete optic atrophy gives a poor outlook. Jefferson and Rosenthal[70] report two cases of massive spontaneous infarction in a pituitary adenoma. This diagnosis should always be suspected when a patient with pituitary dysfunction

suddenly develops signs of an intracranial catastrophe—subarachnoid hemorrhage, meningitis, blindness, ocular palsies, or collapse with coma. Both patients showed sellar changes on x-ray examination. An interesting report by Bakay [71] states that the great majority of pituitary adenomas with extrasellar extension show increased cerebrospinal fluid protein levels. The same relationship does not hold in other tumors of the sellar region, although increased protein is found in the majority. Suprasellar tumors do not fulfill Cushing's triad of primary optic atrophy, bitemporal field defects, and a normal sella according to Fanta.[72] Only 2 of 22 cases demonstrated bitemporal defects. All the others had an asymmetrical development of visual field loss, most often beginning unilaterally. Hirsch [73] reports a study of 23 patients with craniopharyngioma. Four patients showed homonymous hemianopsia, ten had temporal or bitemporal anopsia, others had irregular fields with central scotomata. Calcification appeared on x-ray examination in five patients, and all but three had an enlarged sella. Total excision is possible in some cases of craniopharyngioma, according to Kahn.[74] He reports on 12 patients over 40 years of age, none of whom had papilledema, and on 65 patients under 40, 43% of whom showed papilledema or its residuals. This difference is confirmed by his study of the literature. Calcification visible on x-ray examination is four times as likely in the younger group. He believes that if there is reasonable doubt as to the histology of a chiasmal lesion, and a definite diagnosis of pituitary adenoma cannot be made, surgical exploration is preferred to x-ray therapy.

Visual disturbances occurred in 31% of 150 patients with acoustic neuroma, according to Fabricant.[75] Corneal anesthesia on the involved side was found in 84%, spontaneous nystagmus in 83%, and choked disc in 49%. Tinnitus and hearing loss progressing to deafness were found in all the patients, and x-ray examination was positive in only 43%. Another important finding not mentioned in the article is elevation of the cerebrospinal fluid protein level. This occurs in many patients.

The ocular signs of meningiomas are reviewed in detail by Rougier et al.[76] The ophthalmologist may have the responsibility of diagnosing these cases when the tumor is located in the suprasellar region, the olfactory groove, the lesser wing of the sphenoid, or the orbit.

Patients with tumor of the occipital lobe rarely show a homonymous scotoma, according to Bender and Battersby.[77] They find the characteristic field defect to be often a partial or complete anopia, or amblyopia. With special testing methods there may be areas of amblyopia surrounding a localized scotoma and perception of form and color may be affected in the homonymous halffields.

Pseudotumor cerebri is characterized by signs and symptoms of increased intracranial pressure, absence of cytologic and chemical abnormalities in the cerebrospinal fluid, absence of localizing neurological signs, and normal ventriculograms, reports Smith.[78] He reviews 36 cases with complaints of headache in 64%, blurred vision in 42%, and diplopia in 28%. Abducens palsy was found in 31%, and in 42% the ventricles were smaller than normal. Subtemporal decompression was done in 44% where papilledema was associated with evidence of visual deterioration, although Hollenhorst points out in a discussion of the paper that fluid and salt restriction with a reduction diet are equally as effective. Sitchevska [79] points out that the outstanding finding of this disease is bilateral papilledema without intracranial tumor often occurring in obese young females. The cause is unknown but is probably an endocrine disturbance and electrolyte imbalance. The importance to ophthalmologists is that vision may be impaired by long continuing papilledema. Wertheimer et al.[80] note after discussing 12 patients with this disease that conservative treatment is indicated in the presence of papilledema, and doubtful elec-

troencephalograms when ventriculography does not give evidence of intracranial tumor.

Lesions of Visual Radiations

Interest continues in the relation of temporal lobe resection to visual field loss. Hullay [81] reported 50 surgically treated temporal epileptic patients, with a persistent homonymous upper quadrantic visual field defect in 20 cases. The field loss did not correlate with the amount of lobe resection. Konzelmann [82] showed 20 patients in his protocols in whom 16 had a field defect. The variable amount of quadrant loss does not correspond to the extent of temporal lobe resection in his drawings. Forty-one similar patients are reported by Van Buren and Baldwin.[83] In five cases there were no detectible field changes even though the tip of the temporal horn of the lateral ventricle and its surrounding white substance were removed in every case. Variable quadrant defects appeared in the remainder. In 10 of these the defects were congruous, whereas in the rest they were incongruous with the larger defect on the side of the lesion. Falconer and Wilson [84] report a further article on the subject since last year's review. Thus the classical concept of Meyer's loop continues to fade.

Infections

An unusual case of Vogt-Koyanagi syndrome with an initial diagnosis of intracranial tumor is reported by Gregory.[85] Bilateral papilledema with blind spot enlargement preceded a severe bilateral uveitis by two months. The reason for the papilledema was obscure. Gibbs [86] notes that an apoplectiform type of visual loss in chiasmal arachnoiditis is similar to the reaction in spinal cord lesions with chronic spinal leptomeningitis. The diagnosis in his case was made by exclusion, not direct surgical visualization. Three cases of sarcoidosis of the central nervous system are analyzed by Matthews.[87] In one patient, residual pupillary changes strongly resemble an Argyll Robertson pupil. He believes that the possibility of past sarcoidosis should be considered in patients with an unexplained Argyll Robertson pupil.

Orbit and Middle Cranial Fossa; Injuries

The neuro-ophthalmological importance of lesions in the "sphenosellar recess" is emphasized by Smith.[88] This retro-orbital region is a neurological crossroad comparable with the cerebellopontine angle. The clinical onset may be insidious with only loss of vision and visual field defects present at first. Continued observation is important and indications for surgery which appear are uncontrollable pain, progressive threat to vision in *both* eyes, and increased intracranial pressure. Campion [89] points out that unilateral exophthalmos from intracranial lesions is due to a relatively few lesions, the most common being meningioma of the Exophthalmos may be the presenting symptom in some cases. An unusual type of unilateral exophthalmos due to infratemporal subdural hematoma is presented by Pfeiffer.[90] Where the hemorrhage occurs in the formative years when the skull is malleable, typical x-ray changes are evident and forward encroachment on the orbit produces proptosis. There may also be fullness in the temporal region.

Fargó [91] discusses 18 patients with epidural hematomas found in a series of 6,045 head injuries. Pupillary changes varied with the stage and rapidity of rise of intracranial pressure. A homolateral dilated fixed pupil was seen early in only two cases, nine others had gradual development of a dilated fixed pupil, while three patients had no anisocoria, and in four others a direct light reaction was present in both eyes.

The ocular findings in 47 cases of subdural hematoma, subdural hygroma, and subarachnoid hemorrhage in infants and young children are analyzed by Hollenhorst and Stein.[92] Sixty per cent had ocular findings, most frequently retinal and subhyaloid hemorrhage, less often extraocular muscle palsy or papilledema. Retinal and subhyaloid hemorrhages are a reflection of sudden increases in intracranial pressure, with

papilledema less likely than in adults because of open fontanels and separated sutures. Prognosis for ultimate binocular vision is not uniformly good among those infants with ocular abnormalities at the time of initial examination, especially in those with head injury.

Ocular Motility

Both basic and clinical information on ocular motility has appeared during the year. Wagman et al.[93] reported detailed stimulation experiments on the occipital lobe of the macaque. The most frequent types of eye movement obtained from the posterior parts of the hemisphere are contralateral oblique downward conjugate deviation and contralateral oblique upward deviation. Stimulation of dorsal and dorsolateral surfaces produces downward contralateral deviation, whereas upward contralateral deviation results from stimulation of the inferior lateral surfaces. Cranial nerve function after total cerebral hemispherectomy in the monkey is reported by White and MacCarty.[94] Within 12 hours after operation, all the animals showed complete homonymous hemianopsia, nystagmus, and conjugate lateral deviation toward the operative side. The pupils were equal in size with diminished light reflexes. The hemianopsia was permanent, the nystagmus persisted less than two weeks, Wernicke's pupillary sign appeared, and the conjugate deviation was absent in the majority of animals by two months.

An unusual application of supranuclear lesions is described by Wycis and Spiegel,[95] who produced stereotactic lesions of the periaqueductal gray matter, in an attempt to alleviate the oculogyric crises of Parkinsonism. Transient impairment of upward gaze resulted.

A further case of congenital ocular motor apraxia is added to the literature by the Keiners.[96] They feel that the optical component of gaze tonus is so underdeveloped that the nonoptical component has remained dominant. The basic neuroanatomy of ocular motility of supranuclear type is reviewed by Vila Coro.[97] Lemmen et al.[98] describe a series of patients with forced horizontal conjugate deviation following lesions of the frontal cortex, internal capsule, rostral midbrain, and after occipital lobectomy. One patient showed proof of reciprocal innervation of the ocular muscles from the frontal eye field. Another patient followed by Lemmen and Davis[99] gave clinical evidence supporting basic experimental animal work on the course of horizontal gaze fibers through the brainstem.

Smith and Cogan[100] reviewed 58 cases of internuclear ophthalmoplegia, 29 unilateral, and 29 bilateral. The unilateral type occurs more frequently in older men and may be due to vascular disease or diabetes. The bilateral type occurs equally in men and women and at any age, and the usual cause is multiple sclerosis. Prognosis for life is poor in the unilateral variety. Three cases of anterior internuclear paralysis are reported by Ethelberg and Vaernet[101] in supratentorial space-taking lesions. They believe the cause is dysfunction of the brainstem following herniation of the midbrain into the tentorial notch and impaction of the medulla into the foramen magnum.

In an analysis of 235 primary brain tumor cases, Parsons[102] found disturbance of ocular motility in 25%. The oculomotor nerve was involved almost twice as often as the abducens. In tumors of the convexities, palsy was usually unilateral, the third nerve was more frequently affected, and multiple nerve involvement was not encountered. In temporal lobe tumors, oculomotor palsy was three times as frequent as abducens involvement. Rucker[103] reviews 1,000 cases of ocular motor paralysis. Head injuries were responsible for 17%; an equal number were due to brain tumors, nearly half of which were metastatic. Vascular disease was thought responsible in 15%, and aneurysm of the circle of Willis in 11%, the majority involving the third nerve. The cause was not found in 28%.

The existence of diabetes mellitus should be excluded in every case of paralysis of the ocular muscles where the cause is not

obvious. Snydacker [104] presents six such cases, and notes that the prognosis for recovery is good with adequate diabetic control. We are reminded that ophthalmic herpes zoster can produce extraocular muscle palsies by Schirmer,[105] who noted a trochlear paralysis in one patient, an oculomotor palsy in another.

Myasthenia gravis in childhood should be kept in mind in examining strabismus patients, according to Costenbader.[106] The juvenile type may occur from one week of age to 17 years and may include bilaterally symmetrical ocular muscle pareses in 66% of patients. Congenital myasthenia in four sons of a family is reported by Walsh and Hoyt.[107] Ptosis responded to prostigmine, but there was only partial or mild improvement in the other eye muscles. These cases are not clearly examples of either true myasthenia gravis or of muscular dystrophy. Huber [108] reports that electromyography has been an important additional test in the early diagnosis of ocular myasthenia. Return of the myogram to normal occurs with Tensilon (edrophonium chloride) administration.

The association of abnormal eye movements with myoclonus is noted by Cooper.[109] Of 37 cases, 17 had nystagmus, 6 had true ocular myoclonus, described variously as vertical, rotary, horizontal, or pendular oscillations in association with movements of other structures. In evaluation of such eye movements, one should look for palatal or associated myoclonus.

A skew deviation or Hertung-Magendie strabismus followed a severe head injury in a patient reported by Piper.[110] He points out the similarity to bilateral trochlear paralysis.

The evidence continues to point to consideration of the usual progressive external ophthalmoplegia as a localized form of muscular dystrophy. Panst et al.[111] noted the associated affection of shoulder and facial muscles detected only by careful clinical examination, and confirmed the diagnosis by biopsy and electromyography of the eye muscles. Kirschbaum and Holland [112] found normal motor end plates in the degenerated fibers of the extraocular muscles, excluding a nuclear amyotrophy. Nicolaissen and Brodal [113] found histologic changes similar to those in cases of muscular dystrophy in a woman with gradual development of complete external ophthalmoplegia. However, the Meobius syndrome appears due to a supranuclear lesion according to Van Allen and Blodi.[114] They used electromyography to demonstrate the defect and their findings are in contrast to other authors who have recently reiterated the opinion of some early observers that the basic defect may be peripheral and in the muscles.

Sensory Affections

Raeder's paratrigeminal syndrome is a clinical picture in which ptosis and miosis suddenly appear coincident with pain usually in and around the eye, according to Smith.[115] It is more common in males and is due to a lesion at the region of the internal carotid and trigeminal nerve. In contrast to Horner's syndrome, there is no anhidrosis, and the prognosis is much more benign. Ford and Walsh [116] note that the first symptom is headache above the eyes severe enough to awaken the patient early in the morning. The headache may occur every morning for weeks or months, and shortly after the onset the homolateral lid begins to droop and the pupil becomes smaller. After some months, the lid and pupil return to normal. Because of the usually clear history of past morning headaches, the authors believe that Raeder's syndrome is a somewhat unusual result of a series of severe and frequent migrainous headaches with edematous changes in the internal carotid occasionally resulting in damage to sympathetic fibers in its sheath at the base of the middle fossa.

A thorough review of the anatomy, mechanisms, and types of facial pain is presented by Smith.[117] He describes the use of intravenous stilbamidine isethionate for trigeminal neuralgia. This has a selective

neurotropic action to produce a trigeminal neuropathy consisting of hypesthesia and paresthesia but no motor paralysis. The drug action is slow but prolonged and self-limited paresthesias are troublesome in about 20% of cases. Ruge et al.[118] review a series of 637 patients treated for trigeminal neuralgia. They prefer selective preganglionic neurotomy under local anesthesia to allow sparing of the sensory innervation to the eye where possible. Such sparing was possible in 65 of the 627 preganglionic sections performed. Postoperative follow-up of 513 patients disclosed conjunctival infections in 39, corneal ulceration in 19, and enucleation became necessary in 6. They believe corneal ulceration occurs only after direct trauma to an insensitive cornea rather than from trophic loss independent of injury. Meticulous care of the denervated eye is recommended.

The association of ophthalmic herpes zoster with contralateral hemiplegia is reported by Anastasopoulos et al.[119] They believe that the vessels in the region of the Gasserian ganglion may be the site of an arteritis which leads to a vascular accident in the ipsilateral hemisphere. The section of spinothalamic and quintothalamic tracts at the midbrain level by stereotactic methods is reported by Wycis and associates[120] in the treatment of post herpetic trigeminal neuralgia. Three of four cases so treated have been at least partially relieved of pain. No permanent effects on oculomotor nerve function resulted even though they may possibly be affected by the treatment.

To the ophthalmologist wishing to review the present concepts of diagnosis and treatment of vascular headaches, the article by DeJong[121] is recommended. He points out that a cerebral aneurysm should be suspected in any patient suffering from recurrent unilateral headaches which always occur on the same side. In migraine, the other side is occasionally involved. Relief of the aneurysmal headache by a vasoconstricting agent may lead to an incorrect diagnosis of migraine. Kunkle[122] noted that the cause of vasodilatation in migraine has not been defined, and hypothesized that acetylcholine may be the chemical agent responsible for relaxation of the arterial wall. He found an acetylcholine-like substance in the cerebrospinal fluid of five out of nine patients during headache of a migraine type.

Cluster headaches is the term preferred by Friedman and Mikropolous[123] for the syndrome variously described as atypical facial neuralgia, Sluder's headache, or Horton's headache. The attacks occur in clusters of one to three paroxysms per day in bouts of from four to ten weeks. Prodromata are rare, the pain is stabbing or throbbing, and associated manifestations are nasal congestion, lacrimation, and ocular injection. Pain is located in the orbit or frontotemporal region. They believe vasodilatation of external carotid branches is causative and recommend ergotamine for treatment.

Scintillating scotoma is an entity commonly existing by itself, according to Miles.[124] He relates the symptoms to reaction in the calcarine artery and feels that they confirm current theories of cortical cytoarchitecture. They may occur independently, or as an aura to migraine which can be considered a more extensive degree of the same vasomotor disease. When scintillating scotoma begins at 60 years or older, there is danger of permanent cortical changes with hemianopsia due to superimposed arteriosclerosis.

Autonomic Ocular Functions; Pupil

The pupil undergoes rapid reflex dilatation by four mechanisms according to Loewenfeld.[125] These are active sympathetic innervation of the dilator muscle, inhibition of the oculomotor nucleus, an adrenergic substance carried by the blood, and adrenal epinephrine arriving at the eye 12 to 15 seconds after the start of stimulation. The mechanism of pupillary dilatation by psychosensory stimulation uses the same motor apparatus as sensory reflex response.

Russell [126] found that neither stimulation nor blocking of the sympathetic innervation had any significant effect on the refraction of the eye and concluded that sympathetic control of visual accommodation is not necessary in man.

The most common site of interruption of the sympathetic pathway in the production of Horner's syndrome is in the sympathetic trunk and the postganglionic fibers before they course intracranially. Giles and Henderson [127] also report that neoplasia, more often malignant, is the most common cause, especially in sympathetic trunk lesions. Trauma and vascular disease are more frequent etiologies in anterior spinal root and brain stem levels. Horner's syndrome is most common in the older age groups, and malignancies are more likely over age 50. In studying the Claude Bernard (Horner's) syndrome, Bonnet [128] finds that localization of the cause may not be simple. In some instances the lesion may be at some distance from the sympathetic pathway. O'Doherty and Green [129] report that an ipsilateral Horner's syndrome was observed in 12 of 18 patients with verified carotid thrombosis. Anhidrosis was usually lacking since the thrombus was above the bifurcation in most instances. They conclude that ptosis and miosis in association with contralateral hemiparesis or other neurologic deficit suggest an internal carotid occlusion on the side of the eye signs. If anhidrosis is also present, either the common or external carotid arteries are involved, or no lesion can be demonstrated. The occurrence of congenital hereditary Horner's syndrome is reported in five members of a family by Durham.[130]

Huerkamp [131] examined 103 patients with tonic pupils; 74% were females and the condition was bilateral in 30% of the cases. The tendon reflexes were abnormal in 62%. He believes that the tonic pupil may be due to stimulation or increased tone of the pupillary sympathetic supply, since associated vegetative symptoms are attributable to sympathetic rather than parasympathetic disorders. The patellar reflexes in patients with tonic pupils were analyzed by Vojíř.[132] In classical Adie's syndrome the knee jerk was areflexic or showed slower decontraction; in less typical or indeterminate forms of tonic pupil the relaxation of the patellar reflexes was also slower; in some cases the knee jerks could not be distinguished from those of tabes dorsalis in spite of negative serology. A disorder of accommodation very similar to that of the pupil was reported by Russell,[133] who studied 15 patients with the Holmes-Adie syndrome. He measured the range of accommodation and response to pilocarpine and found ciliary muscle contraction delayed and a heightened sensitivity to pilocarpine. There was a significant correlation between the sensitivity of the ciliary muscle and the sphincter of the pupil.

A case of tonic pupil resulting from varicella is reported by Monod,[134] who believes it was due to encephalitis with involvement of the midbrain. The same disease resulted in mydriasis in a patient studied by Clavel,[135] who also noted reports of acute bilateral optic neuritis, oculomotor palsy, and papillitis after varicella infection.

The thyroid patient with unilateral lid retraction, no significant exophthalmos, and normal ocular motility does not show hypersympathetic tone according to McLean and Norton.[136] Stellate ganglion block produces a Horner's syndrome, but does not relieve the lid retraction, and electromyography of the levator shows no increase of activity. They conclude that the condition is not innervational in origin, but secondary to changes in the levator muscle in patients with thyroid dysfunction.

Visual Cortex; Frontal Lobes

Cortical blindness was reported by Hoyt and Walsh [137] in a patient with cerebral anoxia following cardiac arrest. Cardiac massage followed by hypothermia preceded the discovery of blindness by a number of days. The patient had agnosia for the blindness, but partial visual recovery ensued. The isolated damage of the occipital

cortex was thought due to the hypothermia which spared other cortical areas less sensitive to anoxia. Madow [138] studied a patient with the classic triad of cortical blindness—complete visual loss, normal pupillary responses, and normal fundi. Arteriosclerosis had resulted in softening of both occipital lobes as shown at autopsy.

The false hope for the blind in recently publicized experiments involving occipital cortex electrodes is exposed by Shipley.[139] Such stimulation creates only a typical corticogenic phosphene but does not supply the basis for differentiation between two patterns simultaneously.

By observing the ocular changes in man following transorbital leucotomy, transfrontal leucotomy, and topectomy, Čavka [140] presents evidence of basic frontal lobe function. The main neuro-ophthalmic symptoms produced by operative lesions of the prefrontal area are anisocoria, conjugate deviation, and horizontal divergence. Less frequently, convergence, vertical divergence, and saccadic movements, as well as nystagmus are observed. All symptoms last for only a few hours after operation except for the anisocoria which may appear as late as two weeks after surgery and may last over a month.

Nystagmus

Bárány considered optokinetic nystagmus as a fixation reflex, while Ohm thought that harmonic stimuli from cortical and subcortical nerve cells, especially of Deiter's nucleus, played the principal role according to Mackenson.[141] He believes that both views can be reconciled, with the slow duction movement explained as a fixation reflex, while the quick phase is probably governed by impulses from higher centers. By electro-oculography Mackenson and Wiegmann [142] demonstrated a definite after-nystagmus following optokinetic stimulation. It generally begins after a prolonged deviation of the eyes in the direction of the slow phase, and all values (amplitude, frequency, phase velocity) become smaller with the duration of the after-nystagmus. The diagnostic value of optokinetic after-nystagmus must await further study.

Pasik et al.[143] report the effects of cerebral lesions on optokinetic nystagmus in monkeys. Bilateral occipital lobectomy eliminated optokinetic nystagmus, but all other lesions including serial unilateral resections of one hemisphere failed to produce a defect. The results suggest that a minimal amount of vision is necessary to obtain an optokinetic response, that homonymous loss of vision does not interfere with optokinetic nystagmus in either direction, and that there are no special "cortical centers" for such nystagmus in the monkey. By assessing the effects of brainstem lesions on optokinetic nystagmus in monkeys, Teng et al.[144] conclude that the impulses for optokinetic nystagmus and for spontaneous deviation of the eyes are mediated through a common or identical descending pathway through the brain stem.

Nicolai [145] reports a study of optokinetic responses in patients with unilateral amblyopia and noted distinct differences. Further studies will be necessary to prove whether such differences are an inconstant symptom of high-grade strabismic amblyopia.

Reinecke and Cogan [146] studied optokinetic response as a measure of visual acuity using progressively smaller lines or an increased distance from the stimulus. The results correlated well with Snellen acuity measurements.

A study of "end-position" nystagmus by Blomberg [147] in 25 patients with Ménière's syndrome, 17 with signs of unilateral space-taking lesions, and 6 with vertigo, showed that such nystagmus is not normal but a sign of disturbed equilibrium of the oculomotor system. When Evipan (hexobarbital sodium) is used, the nystagmus becomes more conspicuous, and difference between the two sides may aid in recognition of a lesion of the oculovestibular system.

Stanley-Jones [148] explains miner's nystagmus, as well as the oculogyric crises of

Parkinson's disease, by the cybernetic principle which explains an oscillation as a failure of negative or stabilizing feed-back. The goal of binocular fixation is due to an intrinsic feed-back from the macular cones. This has failed in miner's nystagmus and the failure is due to disuse atrophy of the fixation reflexes caused by constant staring at the featureless blank of the coal-face. Substitution of the rods brings an extrinsic circuit into play which is used to bring back the eyes from their rolling excursions under control of the peripheral vision.

Two cases of seesaw nystagmus are added by Jensen [149] to the previous three in the literature. The pathogenesis is unknown, but this rare form of nystagmus occurs in the presence of brainstem lesions, particularly if there is involvement of the superior parts of the median longitudinal fasciculus, perhaps in the posterior commissure area. Both cases reported had transient signs of arterial thrombosis in the brainstem.

Electro-oculography was used by Herberg and Schilf [150] to study a patient with voluntary pendular nystagmus. The high frequency of movement resembled a tremor of other skeletal muscles.

Retraction nystagmus has been reported in only 25 cases in the past 50 years, according to Amidei.[151] His patient had acute disseminated encephalomyelitis, and showed upward gaze paralysis and horizontal nystagmus in addition to the nystagmus retractorius. Thiébault et al.[152] believe that such nystagmus should direct attention to the vicinity of the aqueduct of Sylvius, the region of the oculomotor nuclei, and the related association pathways. Parinaud's syndrome of impaired upward gaze is almost always present as well.

Spontaneous attacks of rotary nystagmus were observed by Meredith and Adams [153] in a patient with a cholesteatoma of the left cerebellopontine angle. There were associated slight deafness in the left ear, weakness of the left vocal chord, unsteadiness in gait, and intermittent muscular twitching of the left face. At the time of each attack of nystagmus, spontaneous vertigo and a sensation of movement occurred.

Visual Fields

The multiple-pattern method of visual field examination is brought up to date by its originators, Harrington and Flocks.[154] They emphasize care in details of technique, and are working to prepare even better test patterns. The use of the lid of the screening instrument as a short radius tangent screen is recommended for immediate checking whenever there is an abnormal response in the multiple pattern test.

Blum, Gates, and James [155] found that in 1,892 consecutive patients in whom both peripheral and central fields were performed, only 25 fields representing 22 patients, showed positive peripheral and negative central fields. In not one case did the peripheral fields provide anything vital or in any way assist in the management or diagnosis. Although not advocating the abolition of the perimeter, they question the value of its routine use over the tangent screen.

The use of a special 750 mm. radius bowl perimeter to cover the intermediate isopters between 25 degrees and 50 degrees is described by Chamlin.[156] He anticipates that some diseases interfering with the intra- or extraocular visual pathways may show the earliest or most marked visual field defects in this intermediate zone. We will await further reports. The use of multiple targets in tangent screen examination is reported by Zeller.[157] The advantage in comparing two targets on either side of the vertical meridian is definite, and indicates that true macular sparing must be unusual. Zeller uses multiple targets on the felt-covered paddle devised originally by Chamlin. Lytton [158] describes a simple apparatus which he has devised to obtain steadier fixation during field testing. In a study of the visual fields in healthy normal sighted subjects, Hager [159] notes that aging limits the visual fields. He describes his method

of assessing the degree of this functional change.

Mooney [160] presents some interesting comments on visual field defects. He believes that a bitemporal hemianopsia with normal discs suggests a retrochiasmal lesion unsuitable for surgery. A central scotoma in one eye with a temporal field defect in the other suggests a space-taking lesion in the chiasmal region. A bitemporal hemianopsia, predominantly non-scotomatous, with some disc pallor, suggests that at least some of the tumor is prechiasmal, displacing the nerves, and surgery is indicated. He does not feel that notching of the nerves and chiasm pushed up against the anterior cerebral arteries gives convincing evidence for the field defects encountered.

Bilateral homonymous hemianopsia may occur simultaneously or with a separating time interval, according to Rucker and Kearns.[161] The cause may be either two separate vascular accidents of both optic radiations or visual cortices, but in simultaneous bilateral loss the offending lesion is occlusive disease in the basilar artery or its branches. The rarity of incongruous homonymous hemianopsia from lesions of the optic tracts is noted by the same authors.[162] Such defects result from the same lesions of the chiasmal region which ordinarily elicit bitemporal defects. Instead of expanding in the midline, such lesions have extended to one optic tract.

DuBois-Poulsen and Magis [163] review 13 cases in which unusual blind spot enlargements did not correlate with visible fundus change or disc swelling. The syndrome is associated with lesions in the chiasmal area, and is often associated with distension of the anterior ventricular system, more often the lateral ventricle. Concentric contraction of the visual fields and inversion of isopters were studied by Kluyskens [164] who reports that real malingering, the wish not to see, exaggeration of symptoms in patients with postconcussional syndrome, and poor attention were the main causes for the abnormal fields. The performance of a psychoneurotic person was often quite similar to that of a malingerer.

The seventh edition of Traquair's classic on perimetry, now rewritten by Scott,[165] has appeared since last year's review. Much new material has been added, and the book is more readable than before.

Miscellaneous

A comprehensive monograph on premature synostosis of the cranial sutures has been presented by Bertelsen.[166] He studied 219 patients, and 171 were used for an analysis of eye findings. Papilledema was present in 26, optic atrophy in 33. The incidence of optic nerve involvement was 80% in craniofacial dysostosis, 35.9% in oxycephaly. He believes that optic nerve damage results from increased intracranial pressure rather than narrowing of the optic canals, and appears to develop only in oxycephaly, craniofacial dysostosis, and acrocephalosyndactyly.

Uihlein and Rucker [167] review the clinical entities producing acute visual failure and necessitating prompt neurosurgical intervention. Cases presented include infarction of a pituitary adenoma, hemorrhage into an optic nerve hemangioendothelioma, internal carotid aneurysm, and craniopharyngioma. They emphasize the need for a complete and accurate medical, neurologic, and ophthalmologic examination for early diagnosis.

The occurrence of transient blindness after epileptic attacks is reported by Fiume.[168] He attributes the process to hypoxia of the occipital areas resulting from disturbances of the cerebral circulation due to the repeated convulsive attacks.

A total of 13 cases of Cogan's syndrome (non-syphilitic interstitial keratitis and vestibuloauditory symptoms) are reported by Norton and Cogan.[169] There is still no definite proven etiology and no effective treatment. Six patients however have manifested evidence of systemic cardiovascular disease. It is believed that the oculoauditory findings are only one phase of a systemic

disturbance related to the cardiovascular system.

Interesting observations are reported by Wania and Walsh [170] on a child in whom almost the entire cerebellum was removed in treatment of an encephalocele. Two years later there were no ocular or general cerebellar signs. The absence of such signs conforms to present knowledge concerning cerebellar removals in animals. Abnormal functioning of the body after cerebellar removal depends on abnormal functioning of the remaining central nervous system, and nystagmus does not develop if the floor of the fourth ventricle is not injured during extirpation.

Brickner [171] noted a gross inequality of the palpebral fissures in 92% of 51 patients with multiple sclerosis. The palpebral narrowing was usually due to ptosis; often with homolateral smaller pupil. He studied earlier pictures of these patients and found that the sign was present in many as far back as infancy, before the onset of multiple sclerosis. In a control study, less than 30% inequality of fissures was found. He feels this is probably a mild Horner's syndrome in most cases.

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REFERENCES

1. Hollenhorst, R. W.: Diseases of the Retina and Optic Nerve, A.M.A. Arch. Ophth. 61:789-837 (May) 1959.

2. Leinfelder, P. J.: The Pathogenesis of Papilledema, Digest Ophth. & Otolaryg. 21:130-132 (Jan.-April) 1959.

3. Glew, W. B.; Kearns, T. P.; Rucker, C. W., and Essex, H. E.: The Experimental Production of Papilledema, A.M.A. Arch. Ophth. 60:1074-1079 (Dec.) 1958.

4. Korein, J.; Cravioto, H., and Leicach, M.: Reevaluation of Lumbar Puncture: A Study of 129 Patients with Papilledema or Intracranial Hypertension, Neurology 9:290-297 (April) 1959.

5. Huber, A., and Cagianut, B.: The Differential Diagnosis of Papilledema in Malignant Hypertension and Choked Disc, Ophthalmologica 135: 412-426 (May-June) 1958.

6. Chamlin, M.: Aqueous Floaters in the Differential Diagnosis of Papillitis and Papilledema, A.M.A. Arch. Ophth. 61:37-44 (Jan.) 1959.

7. Lubeck, M. J.: Papilledema Caused by Iron-Deficiency Anemia, Tr. Am. Acad. Ophth. 63:306-310 (May-June) 1959.

8. Oliver, T. K., Jr., and Havener, W. H.: Eye Manifestations of Chronic Vitamin A Intoxication, A.M.A. Arch. Ophth. 60:19-22 (July) 1958.

9. Starr, G. F.; Stroebel, C. F., Jr., and Kearns, T. P.: Polycythemia with Papilledema and Infratentorial Vascular Tumors, Ann. Int. Med. 48:978-986 (May) 1958.

10. Halpern, L.; Feldman, S., and Peyser, E.: Subarachnoid Hemorrhage with Papilledema Due to Spinal Neurofibroma, A.M.A. Arch. Neurol. & Psychiat. 79:138-141 (Feb.) 1958.

11. Lasco, F.; Arseni, C.; Opresco, I., and Nicolesco, M.: The Clinical Significance and Etio-Pathogenesis of the Foster Kennedy Syndrome in the Light of Neuro-Surgical Data, Neuro-Chirurgie 4:124-129 (April-June) 1958.

12. Bynke, H.: The Syndrome of Foster Kennedy, Acta ophth. 36:129-140, 1958.

13. Petersen, H. P.: Pits or Crater-like Holes in the Optic Disc, Acta ophth. 36:435-443, 1958.

14. Francois, J., and Verriest, G.: Drusen of the Papilla, Ophthalmologica 136:289-325, 1958.

15. Igersheimer, J.: Serious Visual Troubles Caused by Unusual Circulatory Disturbances in the Region of the Optic Nerve, Tr. Am. Ophth. Soc. 56:275-287, 1958.

16. Klíma, M.; Petr, R.; Steinhartová, L., and Rehák, S.: Surgical Treatment of Prechiasmatic Neuritis Complicated by Incarceration of the Intracanalicular Segments of the Optic Nerves, Ophthalmologica 136:161-174, 1958.

17. Carroll, F. D.: Optic Nerve Lesions: Differential Diagnosis, Survey Ophth. 3:293-296 (Aug.) 1958.

18. Rosselet, E.: Retrobulbar Neuritis and Brain Tumor, Confinia neurol. 18:363-369, 1958.

19. Hierons, R., and Lyle, T. K.: Bilateral Retrobulbar Optic Neuritis, Brain 82:56-67 (March) 1959.

20. Hamilton, H. E.; Ellis, P. P., and Sheets, R. F.: Visual Impairment Due to Optic Neuropathy in Pernicious Anemia: Report of a Case and Review of the Literature, Blood 14:378-385 (April) 1959.

21. Skillern, P. G., and Lockhart, G.: Optic Neuritis Associated with Uncontrolled Diabetes Mellitus, J. Lab. & Clin. Med. 52:947 (Dec.) 1958.

22. Sasso, B.: Optic Neuritis Following Varicella, Ophthalmologica 136:157-160, 1958.

23. De Vincentiis, M.: The Probability of Viral Etiology in Cases of Retrobulbar Optic Neuritis, Arch. ottal. 61:209-216 (May-June) 1957.

24. Kepes, J., and Remenár, L.: Disseminated Encephalitis Beginning with Symptoms of Lactation Neuritis of the Optic Nerve, Confinia neurol. 18:12-20, 1958.

25. Petit - Dutaillis, D.; Schiff - Wertheimer, Mme.; Aubry, M., and Metzger, J.: Syndrome of Compression of the Optic Nerve By a Latent Sphenoid Mucocele, Neuro-Chirurgie 4:81-94 (April-June) 1958.

26. Wagener, H. P.: Gliomas of the Optic Nerve, Am. J.M. Sc. 237:238-261 (Feb.) 1959.

27. Dodge, H. W., Jr.; Love, J. G.; Craig, W. M.; Dockerty, M. B.; Kearns, T. P.; Holman, C. B., and Hayles, L. B.: Gliomas of the Optic Nerve, A.M.A. Arch. Neurol. & Psychiat. 79:607-621 (June) 1958.

28. Weizenblatt, S.: Metastatic Disease of the Optic Nerve, Am. J. Ophth. 47:77-83 (Jan., Pt. 1) 1959.

29. Norton, H. J., Jr.: Adenocarcinoma Metastatic to the Distal Nerve and Optic Disc, Am. J. Ophth. 47:195-199 (Feb.) 1959.

30. Lasco, F.; Nicoleso, M., and Niculiu, I.: Retrobulbar Pseudoneuritis with Intracranial Metastasis, Arch. opht. 19:19-21 (Jan.-Feb.) 1959.

31. Reese, A. B., and Carroll, F. D.: Optic Neuritis Following Cataract Extraction, Am. J. Ophth. 45:659-662 (May) 1958.

32. Rougier, J., and Royer, J.: The Value of Cerebral Angiography in the Diagnosis of Optic Atrophy, Bull. Soc. opht. France, No. 3, pp. 268-271, March, 1958.

33. Manchester, P. T., and Calhoun, F. P., Jr.: Dominant Hereditary Optic Atrophy with Bitemporal Field Defects, A.M.A. Arch. Ophth. 60: 479-484 (Sept.) 1958.

34. Dawson, B. H.: The Blood Vessels of the Human Optic Chiasma and Their Relation to Those of the Hypophysis and Hypothalamus, Brain 81:207-217 (June) 1958.

35. Alpers, B. J.; Berry, R. G., and Paddison, R. M.: Anatomical Studies of the Circle of Willis in Normal Brain, A.M.A. Arch. Neurol. & Psychiat. 81:409-418 (April) 1959.

36. Piper, H. F., and Unger, L.: Inferior Hemianopsia Due to Circulatory Disturbances Affecting the Optic Nerve, Ophthalmologica 134: 169-180 (Sept.) 1957.

37. Sullivan, P. R.; Kuten, J.; Atkinson, M. S.; Angevine, J. B., Jr., and Yakovlev, P. I.: Cell Count in the Lateral Geniculate Nucleus of Man, Neurology 8:566-567 (July) 1958.

38. Pickering, G. W.: The Influence of Vascular Changes in Progressive Failure of Vision, Tr. Ophth. Soc. U. Kingdom 78:295-301, 1958.

39. A Classification and Outline of Cerebrovascular Diseases, Committee of the Advisory Council for the National Institute of Neurological Diseases and Blindness, Public Health Service, Neurology 8:395-434 (May) 1958.

40. Hollenhorst, R. W.: Ocular Manifestations of Insufficiency or Thrombosis of the Internal Carotid Artery, Tr. Am. Ophth. Soc. 56:474-506, 1958.

41. Hollenhorst, R. W.: Ophthalmodynamometry and Intracranial Vascular Disease, M. Clin. North America 42:951-958 (July) 1958.

42. Mones, R.: Ophthalmodynamometry, J. Mt. Sinai Hosp. New York 26:71-77 (Jan.-Feb.) 1959.

43. Van Allen, M. W.; Blodi, F. C., and Brintnall, E. S.: Retinal Artery Blood Pressure Measurements in Diagnosis and Surgery of Spontaneous Carotid Occlusions, J. Neurosurg. 15:19-29 (Jan.) 1958.

44. Spalter, H. F.: Ophthalmodynamometry and Carotid Artery Thrombosis, Am. J. Ophth. 47: 453-467 (April) 1959.

45. Belmonte Gonzales, N.: Clinical Ophthalmodynamometry, Arch. Soc. oftal. hispano-am. 18: 473-807 (June-July) 1958.

46. Mueller, H. K.: The Physical Basis of Ophthalmodynamometry, Arch. chilenos oftal. 39:87-91 (July-Dec.) 1957.

47. Schirmer, R.: The Construction of a New Ophthalmodynamometer, Ophthalmologica 136:413-416 (Dec.) 1958.

48. Crevasse, L. E., and Logue, R. B.: Carotid Artery Murmurs, J.A.M.A. 167:2177-2182 (Aug. 30) 1958.

49. Oldendorf, W. H.: Demonstration of Carotid Occlusion by Small Dose Arteriography, Neurology 8:296-298 (April) 1958.

50. Carvioto, H.; Rey-Bellet, J.; Prose, P. H., and Feigin, I.: Occlusion of the Basilar Artery: A Clinical and Pathologic Study of 14 Autopsied Cases, Neurology 8:145-152 (Feb.) 1958.

51. Millikan, C. H.; Siekert, R. G., and Whisnant, J. P.: Anticoagulant Therapy in Cerebral Vascular Disease-Current Status, J.A.M.A. 166: 587-597 (Feb. 8) 1958.

52. Wagener, H. P., and Hollenhorst, R. W.: The Ocular Lesions of Temporal Arteritis, Am. J. Ophth. 45:617-630 (May) 1958.

53. Parsons-Smith, G.: Sudden Blindness in Cranial Arteritis, Brit. J. Ophth. 43:204-216 (April) 1959.

54. Krayenbühl, H.: Cerebral Venous Thrombosis, Schweiz. med. Wchnschr. 89:191-195 (Feb. 21) 1959.

55. Tyler, H. R., and Clark, D. B.: Neurologic Complications in Patients with Coarctation of the Aorta, Neurology 8:712-718 (Sept.) 1958.

56. Savin, L. H.: Influence of Vascular Changes in Progressive Failure of Vision, Tr. Ophth. Soc. U. Kingdom 78:315-326, 1958.

57. Rhonheimer, C.: About the Symptomatology of Sellar Aneurysms: A Contribution to Differential Diagnosis of the Chiasmal Syndrome, Klin. Monatsbl. Augenh. 134:1-34, 1959.

58. Troupp, H.; Koskinen, K., and af Björkesten, G.: Ophthalmoplegia Caused by Intracranial Aneurysm, Acta ophth. 36:79-86, 1958.

59. Paufique, L.; Rougier, J.; Wertheimer, J., and Allègre, G. E.: Diagnostic and Prognostic

Value of Ocular Signs in Spontaneous Meningeal Hemorrhages, Ann. ocul. 191:561-578 (Aug.) 1958.

60. Rougier, J.; Mansury, and Allègre, G. E.: Oculomotor Paralysis in Aneurysm of the Intracranial Carotid Complicated by Massive Vitreous Hemorrhage, Bull. Soc. opht. France, No. 5-6, pp. 408-410, May-June, 1958.

61. Henderson, J. W., and Schneider, R. C.: The Ocular Findings in Carotid-Cavernous Fistula in a Series of 17 Cases, Tr. Am. Ophth. Soc. 56: 123-144, 1958.

62. Esteban Aranguez, M., and Gallego Tejedor, M.: A Case of Pulsating Exophthalmos Caused by a Carotid-Cavernous Sinus Aneurysm, Arch. Soc. oftal. hispano-am. 18:297-304 (April) 1958.

63. Thiel, H. L.: Ocular Complications of Intracranial Aneurysms, von Graefes Arch. Ophth. 159: 569-581, 1958.

64. Calmettes; Déodati, and Amalric: Evolution of a Pulsating Exophthalmos, Bull. Soc. opht. France, No. 7-8, pp. 480-482, July-Aug., 1958.

65. Enoksson, P., and Bynke, H.: Visual Field Defects in Arteriovenous Aneurysms of the Brain, Acta ophth. 36:586-600, 1958.

66. Walsh, F. B.: Some Ocular Signs of Cerebral Tumors in Children, Clin. Neurosurg. 5:166-176, 1957 (1958).

67. Carbajal, U. M.: Ocular Findings in Brain Tumors in Children, A.M.A. Arch. Ophth. 61: 599-607 (April) 1959.

68. Matson, D. D.: Benign Intracranial Tumors of Childhood, New England J. Med. 259:330-336 (Aug. 14) 1958.

69. Heimbach, S. B.: Follow-Up Studies in 105 Cases of Verified Chromophobe and Acidophile Pituitary Adenomata After Treatment by Transfrontal Operation and X-Ray Irradiation, Acta neurochir. 7:8-155, 1959.

70. Jefferson, M., and Rosenthal, F. D.: Spontaneous Necrosis in Pituitary Tumors, Lancet 1: 342-344 (Feb. 14) 1959.

71. Bakay, L.: Spinal Fluid Protein in Tumors of the Sellar Region, Neurology 8:455-460 (June) 1958.

72. Fanta, H.: The Significance of Eye Findings in Cases of Suprasellar Tumors, Wien. klin. Wchnschr. 70:916-918 (Nov. 14) 1958.

73. Hirsch, O.: Symptomatology and Treatment of the Hypophyseal Duct Tumors (Craniopharyngiomas), Confinia neurol. 19:153-219, 1959.

74. Kahn, E. A.: Some Physiologic Implications of Craniopharyngiomas, Neurology 9:82-90 (Feb.) 1959.

75. Fabricant, N. D.: Acoustic Neuroma, Eye, Ear, Nose & Throat Month. 37:776 (Nov.) 1958.

76. Rougier, J.; Allègre, G. E., and Wertheimer, J.: Ocular Signs of Meningiomas, J. méd. Lyon 39:539-546, 1958.

77. Bender, M. B., and Battersby, W. S.: Homonymous Macular Scotomata in Cases of Occipital Lobe Tumor, A.M.A. Arch. Ophth. 60: 928-938 (Nov.) 1958.

78. Smith, J. L.: Pseudotumor Cerebri, Tr. Am. Acad. Ophth. 62:432-440 (May-June) 1958.

79. Sitchevska, O.: Pseudotumor Cerebri, Am. J. Ophth. 47:215-219 (Feb.) 1959.

80. Wertheimer, P.; Rougier, J., and Wertheimer, J.: Papilledema of Unknown Origin, Bull. et mém. Soc. franç. opht. 71:78-94, 1958.

81. Hullay, J.: Results of 50 Surgically Treated Temporal Epileptic Patients, Acta neurochir. 6: 169-174, 1958.

82. Konzelmann, M.: The Visual Field Loss After Temporal Lobe Resection in 16 Cases with So-Called Temporal Epilepsy, Acta neurochir. 6: 323-339, 1958.

83. Van Buren, J. M., and Baldwin, M.: The Architecture of the Optic Radiation in the Temporal Lobe of Man, Brain 81:15-40 (March) 1958.

84. Falconer, M. A., and Wilson, J. L.: Visual Field Changes Following Anterior Temporal Lobectomy: Their Significance in Relation to "Meyer's Loop" of the Optic Radiation, Brain 81: 1-14 (March) 1958.

85. Gregory, I. D. R.: An Unusual Case of the Vogt-Koyanagi Syndrome, Brit. J. Ophth. 43:113-115 (Feb.) 1959.

86. Gibbs, D. C.: Chiasmal Arachnoiditis, Brit. J. Ophth. 43:52-56 (Jan.) 1959.

87. Matthews, W. B.: Sarcoidosis of the Nervous System, Brit. M.J. 1:267-270 (Jan. 31) 1959.

88. Smith, F. P.: Cranio-Orbital Lesions, J. Neurosurg. 16:277-286 (May) 1959.

89. Campion, G. S.: Unilateral Exophthalmos from Intracranial Lesions, Am. J. Ophth. 47:206-214 (May, Pt. 2) 1959.

90. Pfeiffer, R. L.: Infratemporal Subdural Hematoma as a Cause of Exophthalmos, A.M.A. Arch. Ophth. 61:274-281 (Feb.) 1959.

91. Fargó, I.: Concerning Neurologic Syndromes in Epidural Hematomas, Confinia neurol. 19:118-145, 1959.

92. Hollenhorst, R. W., and Stein, H. A.: Ocular Signs and Prognosis in Subdural and Subarachnoid Bleeding in Young Children, A.M.A. Arch. Ophth. 60:187-192 (Aug.) 1958.

93. Wagman, I. H.; Krieger, H. P., and Bender, M. B.: Eye Movements Elicited by Surface and Depth Stimulation of the Occipital Lobe of Macaque Mulatta, J. Comp. Neurol. 109:169-193 (April) 1958.

94. White, R. J., and MacCarty, C. S.: Cranial Nerve Function Following Total Cerebral Hemispherectomy in the Monkey (Macaca Rhesus), Proc. Staff Meet. Mayo Clin. 34:22-29 (Jan. 7) 1959.

95. Wycis, H. T., and Spiegel, E. A.: Parkinsonism with Oculogyric Crises: Stimulation and Partial Elimination of Periaqueductal Grey and

Mesencephalic Tegmentum (Tegmentotomy), Confinia neurol. 18:385-393, 1958.

96. Keiner, G. B. Y., and Keiner, E. C. J. F.: Congenital Ocular Motor Apraxia, Am. J. Ophth. 46:382-385 (Sept., Pt. 1) 1958.

97. Vila Coro.: Supranuclear Disturbances Which Affect Ocular Motility, Arch. Soc. oftal. hispanoam. 18:968-982 (Sept.) 1958.

98. Lemmen, L. J.; Fisher, E. R., and Davis, J. S.: Forced Horizontal Conjugate Gaze in Man, J. Comp. Neurol. 110:257-269 (Oct.) 1958.

99. Lemmen, L. J., and Davis, J. S.: Horizontal Conjugate Gaze in Brain Stem Lesions, Neurology 8:962-964 (Dec.) 1958.

100. Smith, J. L., and Cogan, D. G.: Internuclear Ophthalmoplegia, A.M.A. Arch. Ophth. 61:687-694 (May) 1959.

101. Ethelberg, S., and Vaernet, K.: Vestibulo-Ocular Reflex Disorders of the Anterior Internuclear Paralysis Type in Supratentorial Space-Taking Lesions: Report of 3 Cases, Acta psychiat. et neurol. scandinav. 33:268-282, 1958.

102. Parsons, T. C.: Extraocular Motor Disturbances in Primary Brain Tumors, A.M.A. Arch. Neurol. & Psychiat. 81:182-188 (Feb.) 1959.

103. Rucker, C. W.: Paralysis of the Third, Fourth and Sixth Cranial Nerves, Am. J. Ophth. 46:787-794 (Dec.) 1958.

104. Snydacker, D.: Diabetic Neuropathy as a Cause of Extraocular Muscle Palsy, Tr. Am. Acad. Ophth. 62:704-708 (Sept.-Oct.) 1958.

105. Schirmer, F.: Ophthalmic Herpes Zoster, Klin. Monatsbl. Augenh. 132:252-253, 1958.

106. Costenbader, F. C.: Myasthenia Gravis in Childhood, Med. Ann. District of Columbia 27:227-230 (May) 1958.

107. Walsh, F. B., and Hoyt, W. F.: External Ophthalmoplegia, Am. J. Ophth. 47:28-34 (May, Pt. 2) 1959.

108. Huber, A.: Myasthenia (Erb-Goldflam's Disease) and Paralysis of Ocular Muscles, Bull. et mém. Soc. franç. opht. 70:216-232, 1957.

109. Cooper, J. C.: Eye Movements Associated with Myoclonus, Am. J. Ophth. 46:205-210 (Aug.) 1958.

110. Piper, H. F.: Bilateral Trochlearis Paresis or Hertwig-Magendie Strabismus, Klin. Monatsbl. Augenh. 132:671-681, 1958.

111. Papst, W.; Esslen, E., and Mertens, H. G.: Ocular Muscle Dystrophy, Klin. Monatsbl. Augenh. 132:691-707, 1958.

112. Kirschbaum, W. R., and Holland, J. J.: Progressive Dystrophy of the External Eye Muscles, Neurology 8:304-306 (April) 1958.

113. Nicolaissen, B., and Brodal, A.: Chronic Progressive External Ophthalmoplegia, A.M.A. Arch. Ophth. 61:202-210 (Feb.) 1959.

114. Van Allen, M. W., and Blodi, F. C.: The Meobius Syndrome: A Case Study with Electromyography of the Extraocular Muscles, Am. J. Ophth. 45:926 (June) 1958.

115. Smith, J. L.: Raeder's Paratrigeminal Syndrome, Am. J. Ophth. 46:194-201 (Aug.) 1958.

116. Ford, F. R., and Walsh, F. B.: Raeder's Paratrigeminal Syndrome: A Benign Disorder, Possibly a Complication of Migraine, Bull. Johns Hopkins Hosp. 103:296-298 (Dec.) 1958.

117. Smith, G. W.: Diagnosis and Treatment of Facial Pain, J.A.M.A. 166:857-866 (Feb. 22) 1958.

118. Ruge, D.; Brochner, R., and Davis, L.: A Study of the Treatment of 637 Patients with Trigeminal Neuralgia, J. Neurosurg. 15:528-536 (Sept.) 1958.

119. Anastasopoulos, C.; Routsonis, K., and Ierodiakonou, C. S.: Ophthalmic Herpes Zoster with Contralateral Hemiplegia, J. Neurol. Neurosurg. & Psychiat. 21:210-212 (Aug.) 1958.

120. Wycis, H. T.; Folkerts, J. F., and Spiegel, E. A.: Treatment of Post-Herpetic Trigeminal Neuralgia by Mesencephalotomy or Combined Mesencephalothalamotomy, Zentralbl. Neurochir. 18:188-201, 1958.

121. De Jong, R. N.: The Treatment of Vascular Headaches, GP 19:147-154 (April) 1959.

122. Kunkle, E. C.: Acetylcholine in the Mechanism of Headaches of Migraine Type, A.M.A. Arch. Neurol. & Psychiat. 81:135-141 (Feb.) 1959.

123. Friedman, A. P., and Mikropoulos, H. E.: Cluster Headaches, Neurology 8:653-663 (Aug.) 1958.

124. Miles, P. W.: Scintillating Scotoma, J.A.M.A. 167:1810-1813 (Aug. 9) 1958.

125. Loewenfeld, I. E.: Mechanisms of Reflex Dilatation of the Pupil, Historical Review and Experimental Analysis, Docum. Ophthal. 12:185-448, 1958.

126. Russell, G. F. M.: The Nervous Control of Visual Accommodation, Clin. Sc. 18:119-124 (Feb.) 1959.

127. Giles, C. L., and Henderson, J. W.: Horner's Syndrome: An Analysis of 216 Cases, Am. J. Ophth. 46:289-296 (Sept.) 1958.

128. Bonnet, P.: Notes on the Study of the Syndrome of Claude Bernard: The Action of the Sympathetic System on the Pupil, Arch. opht. 18: 129-147 (March) 1958.

129. O'Doherty, D. S., and Green, J. B.: Diagnostic Value of Horner's Syndrome in Thrombosis of the Carotid Artery, Neurology 8:842-845 (Nov.) 1958.

130. Durham, D. G.: Congenital Hereditary Horner's Syndrome, A.M.A. Arch. Ophth. 60:939-940 (Nov.) 1958.

131. Huerkamp, B.: The Tonic Pupil as a Sign of Sympathetic Stimulation, Klin. Monatsbl. Augenh. 133:161-179 (Aug.) 1958.

132. Vojíř, R.: Particularities of Patellar Reflexes in Tonic Pupil, Acta psychiat. et neurol. scandinav. 33:490-513, 1958.

133. Russell, G. F. M.: Accommodation in the Holmes-Adie Syndrome, J. Neurol. Neurosurg. & Psychiat. 21:290-296 (Nov.) 1958.

134. Monod, M. F.: Concerning a Case of Tonic Pupil in the Course of Varicella, Bull. Soc. opht. France, No. 11, pp. 754-756, November, 1958.

135. Clavel, M. A.: Unilateral Partial Mydriasis as the Result of Varicella, Bull. Soc. opht. France, No. 11, pp. 756-757, November, 1958.

136. McLean, J. M., and Norton, E. W. D.: Unilateral Lid Retraction without Exophthalmos: A Manifestation of Thyroid System Dysfunction, Trans. Am. Ophth. Soc. 56:327-341, 1958.

137. Hoyt, W. F., and Walsh, F. B.: Cortical Blindness with Partial Recovery Following Acute Cerebral Anoxia from Cardiac Arrest, A.M.A. Arch. Ophth. 60:1061-1069 (Dec.) 1958.

138. Madow, L.: Cortical Blindness, J. Neuropath. & Exp. Neurol. 17:324-332 (April) 1958.

139. Shipley, T.: Problems of Corticogenic Vision, Am. J. Ophth. 47:358-363 (March) 1959.

140. Čavka, V.: Ophthalmoneurologic Symptoms Caused by Lesions of the Frontal Lobes, Am. J. Ophth. 45:883-900 (June) 1958.

141. Mackensen, G.: The Theory of Opto-Kinetic Nystagmus, Klin. Monatsbl. Augenh. 132: 769-780, 1958.

142. Mackensen, G., and Wiegmann, O.: Researches in the Physiology of Optokinetic After-Nystagmus, von Graefes Arch. Ophth. 160:497-509, 1959.

143. Pasik, P.; Pasik, T., and Krieger, H. P.: Effects of Cerebral Lesions upon Optokinetic Nystagmus in Monkeys, J. Neurophysiol. 22:297-403 (May) 1959.

144. Teng, P.; Shanzer, S., and Bender, M. B.: Effects of Brainstem Lesions on Optokinetic Nystagmus in Monkeys, Neurology 8:22-26 (Jan.) 1958.

145. Nicolai, H.: Differences Between Optokinetic Right- and Left-Nystagmus in Unilateral (Strabismic-) Amblyopia, Klin. Monatsbl. Augenh. 134:245-250, 1959.

146. Reinecke, R. D., and Cogan, D. G.: Standardization of Objective Visual Acuity Measurements, A.M.A. Arch. Ophth. 60:418-421 (Sept.) 1958.

147. Blomberg, L-H.; The Significance of So-Called "End-Position Nystagmus" and Its Relation to Nystagmus Produced by Evipan, Acta psychiat. et neurol. scandinav. 33:138-150, 1958.

148. Stanley-Jones, E.: Cybernetics of Ocular Movement, Brit. J. Ophth. 42:595-604 (Oct.) 1958.

149. Jensen, O. A.: Seesaw Nystagmus, Brit. J. Ophth. 43:225-229 (April) 1959.

150. Herberg, H. J., and Schilf, E.: Neurologic Considerations in a Case of Voluntary Pendulating Nystagmus, Klin. Monatsbl. Augenh. 132: 780-790, 1958.

151. Amidei, B.: Retraction Nystagmus, Riv. oto-neuro-oftal. 33:3-25 (Jan.-Feb.) 1958.

152. Thiébault, M. F.; Matavuly, N., and Metzger, O.: Three Cases of Nystagmus Retractorius, Bull. et mém. Soc. franç. opht. 70:50-62, 1957.

153. Meredith, J. J., and Adams, R. A.: Spontaneous Rotary Nystagmus in Unilateral Cholesteatoma of the Cerebellopontine Angle, A.M.A. Arch. Ophth. 60:485-487 (Sept.) 1958.

154. Harrington, D. O., and Flocks, M.: The Multiple-Pattern Method of Visual Field Examination, A.M.A. Arch. Ophth. 61:755-765 (May) 1959.

155. Blum, F. G., Jr.; Gates, L. K., and James, B. R.: How Important Are Peripheral Fields? A.M.A. Arch. Ophth. 61:1-8 (Jan.) 1959.

156. Chamlin, M.: An Isopter in the Intermediate Field of Vision, A.M.A. Arch. Ophth. 61: 608-615 (April) 1959.

157. Zeller, R. W.: Multiple Targets in Visual Field Examination with a Tangent Screen, A.M.A. Arch. Ophth. 60:826-827 (Nov.) 1958.

158. Lytton, H.: Fixation in Perimetry and Campimetry, Brit. J. Ophth. 42:762-763 (Dec.) 1958.

159. Hager, G.: The Visual Field and Its Surrounding Region in Healthy Normal-Sighted Subjects, Klin. Monatsbl. Augenh. 142:656-670, 1958.

160. Mooney, A.: Some Neuro-Ophthalmological Problems, Brit. J. Ophth. 42:129-156 (March) 1958.

161. Rucker, C. W., and Kearns, T. P.: Bilateral Homonymous Hemianopsia: Clinics in Perimetry No. 2, Am. J. Ophth. 47:42-44 (Jan., Pt. 1) 1959.

162. Kearns, T. P., and Rucker, C. W.: Clinics in Perimetry No. 3: Incongruous Homonymous Hemianopsia, Am. J. Ophth. 47:317-321 (March) 1959.

163. DuBois-Poulsen, A., and Magis, C.: Extraordinary Enlargements of the Blind Spot, Independent of Swelling of the Nerve Head, Bull. et mém. Soc. franç. opht. 70:12-24, 1957.

164. Kluyskens, J.: The Inversion of the Visual Fields, an Indication of Malingering, Bull. et mém. Soc. franç. opht. 71:64-77, 1958.

165. Scott, G. I.: Traquair's Clinical Perimetry, Ed. 7, St. Louis, C. V. Mosby Co., 1957.

166. Bertelsen, T. I.: The Premature Synostosis of the Cranial Sutures, Act ophth. Supp. 51, p. 1-176, 1958.

167. Uihlein, A., and Rucker, C. W.: The Neurosurgeon's Role in Acute Visual Failure, A.M.A. Arch. Ophth. 60:223-229 (Aug.) 1958.

168. Fiume, S.: Blindness in Epilepsy, Riv. neurol. 28:43-55, 1958.

169. Norton, E. W. D., and Cogan, D. G.: Syndrome of Nonsyphilitic Interstitial Keratitis and Vestibuloauditory Symptoms, A.M.A. Arch. Ophth. 61:695-697 (May) 1959.

170. Wania, J. H., and Walsh, F. B.: Absence of Ocular Signs with Cerebellar Ablation in an Infant, A.M.A. Arch. Ophth. 61:655-656 (April) 1959.

171. Brickner, R. M.: Inequality of Palpebral Fissures Before and After Onset of Multiple Sclerosis: A Preliminary Report, Bull. Los Angeles Neurol. Soc. 23:178-179 (Dec.) 1958.

Correspondence

THE OCCURRENCE OF GLAUCOMA FOLLOWING OCCLUSION OF THE CENTRAL RETINAL ARTERY

To the Editor:—The highly informative paper by Perraut and Zimmerman in the June issue of the A.M.A. ARCH. OF OPHTH. made me think of the possibility that occlusion of the outlets of Schlemm's canal might be found in glaucomatous eyes with retinal artery occlusion if searched for. Since many of the afflicted patients are suffering from vascular disease, it is conceivable that vascular changes similar to those in the central retinal artery could occur in the vessels surrounding Schlemm's canal. It might not be easy to find these obstructions without special methods such as plate reconstruction models or neoprene casts.

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REMOVING SUPERFICIAL CORNEAL PLASTIC FOREIGN BODIES

To the Editor:—After reading Dr. J. Kessler's letter in the May issue of the A.M.A. ARCHIVES OF OPHTHALMOLOGY, I decided to follow his suggestion for removing superficial corneal plastic foreign bodies with a moistened cotton swab.

Much to my amazement, he is absolutely correct—they can be removed in this manner. My statement that "they will not dislodge with a cotton swab" is not valid.

However, I still prefer and recommend the method described in the original article. When one fills the entire field of the biomicroscope with a cotton swab to remove one or more minuscule foreign bodies, the technique is no quicker, no more effective and by its very grossness is repulsive. It is somewhat akin to a virtuoso performing a pizzicato with mittens or a ballerina executing a pirouette in galoshes—possible, but practically and aesthetically unattractive.

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THE MADDOX-ROD PHENOMENON

To the Editor:—With reference to the article by H. Eggers, "The Maddox-Rod Phenomenon," which was published in the February issue of the ARCHIVES, in which it is stated that the textbooks fail to explain how a cylindrical glass rod can make a light appear drawn out into a line perpendicular to the axis of the rod, Mr. H. H. Emsley, B.Sc., has asked me to inform you that in every edition of his book, "Visual Optics," first published in 1936, this description has appeared.

G. H. GILES, O.B.E.
SECRETARY, British Optical Association.

To the Editor:—On page 413, of the second edition (1939) of H. H. Emsley's "Visual Optics," the following explanation appears:

"The student will understand why, although a positive cylinder produces a real focal line parallel to its axis, the observed streak is perpendicular thereto, in the following way; hold a disc of Maddox rods—at arm's length a metre or so

away from the muscle light. Each rod or groove of the disc will be seen to produce a short focal line parallel to itself. Now slowly approach the disc towards the eye; it will be observed that each focal line blurs out in a direction perpendicular to its length, the blurs ultimately overlapping and forming a long streak perpendicular to the axes of the rods and of a width determined by the diameter of your pupil. On retreating from the light, with the rods close to the eye, the streak lengthens and sharpens somewhat."

I submit that, after reading the above, a student will know no more about the Maddox-rod phenomenon than he did initially. It explains nothing and is merely a description. Incidentally, the size of the observer's pupil has no relationship to the matter.

Mr. Emsley is a recognized world authority on optics, and I have no doubt that he himself, long ago, easily understood how a Maddox rod converts a light into a streak. Unfortunately, he did not clarify this in his book.

HARRY EGGERS, M.D.
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AFTER-IMAGES AND OCULAR MUSCLE PROPRIOCEPTION

To the Editor:—The principal conclusion of M. J. Urist in his article, "After-Images and Ocular Muscle Proprioception," A.M.A. ARCH. OPHTH. 61:230-232 [Feb.] 1959, was that since imagined convergence changes perceived size, after-images must be cerebral.

There are several articles in the literature showing that perceived size depends not only on the retinal stimulus, but also upon real or imagined convergence (P. W. Miles, "The Relation of Perceived Size of Half-Images at the Fusion Level to Projection on the Horopter," *Am. J. Ophth.* 34:1543-1561 [Nov.] 1951). A simpler explanation would be that like perceived size, after-images can be altered as well as inhibited centrally.

The retinal nature of after-images can be simply demonstrated. K. S. Craik (*Nature, London* 145:512, 1940), induced an after-image on noncorresponding areas of his two eyes from a 60 watt bulb in 2 minutes. During the induction, he pressed one eye with his finger so that vision was obliterated by anoxia. The anoxia prevented a cerebral stimulus from that eye. Vision quickly returned, and the positive and negative after-images appeared approximately equal in the two eyes.

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To the Editor:—I am in complete agreement with Dr. Miles' statement that after-images can be altered as well as inhibited centrally.

I do not, however, feel that the experiment he cites proves the retinal nature of after-images. This experiment does not exclude the possibility of cerebral transfer of the after-image. In fact, the Brock-Givner Test, A.M.A. ARCH. OPHTH. 47:779, 1952, is based on the retinal stimulation of only one eye with the nonstimulated eye seeing the after-image.

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THE USE OF A MOHAIR BRUSH IN INTRAOCULAR SURGERY

To the Editor:—Barraquer and Boberg-Ans recently described a technique (*Brit. J. Ophth.* 43:69-77 [Feb.] 1959) whereby injury to the lens may be prevented during intraocular procedures. These authors use a small mohair brush in

their intraocular surgery. Even if the lens is accidently touched they find that no damage is produced by the soft brush either to the lens or any other intraocular structure. In addition, they describe the brush as being a very versatile piece of equipment and in most instances it can satisfactorily do the work of an irrigator, forceps, or iris repositer.

After reading their description, I began using a small mohair brush for intraocular procedures and have found it to be most satisfactory. The brush is readily available at any store selling artist supplies. It is sterilized by boiling for 15 minutes before being used and this does not change the soft texture of the hair. After being sterilized, the brush is dried with a piece of sterile cloth and is then ready for use. The brush is a very effective means of removing blood and clots from the anterior chamber. In this respect I have found it to be most valuable in cases of traumatic hyphema with hypertension where surgery is demanded. It is frequently difficult and hazardous to remove the clots with forceps, but with the brush they can be easily stroked out through the paracentesis incision with no damage to the lens. During cataract surgery the brush may be used to dry the wound, and it is surprising how much fluid or blood it will soak up. It is also very useful in repositing the iris or in widening the pupil when doing a round pupil cataract extraction. Barraquer and Boberg-Ans also found the brush to be very useful in spreading out the conjunctival flap, since they use plasma and thrombin as physiologic glue to hold the flap in place rather than using sutures.

During the past three months, I have used a mohair brush in all cases of intraocular surgery including cataract extractions, glaucoma surgery, and the removal of blood from the anterior chamber in traumatic hyphema. I have had excellent success with the use of the brush and find it is a very useful addition to the instruments used in intraocular surgery.

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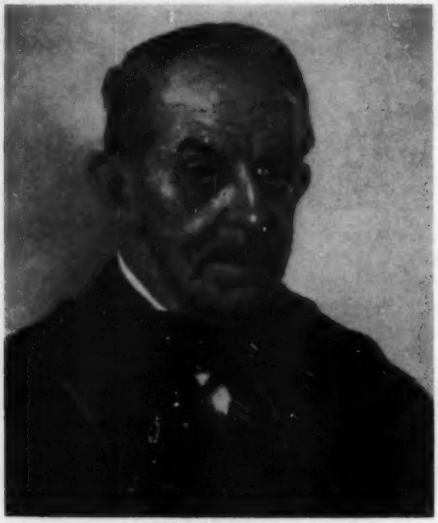
Obituaries

BERNARD SAMUELS, M.D.

1879-1959

Dr. Bernard Samuels of New York, President of the XVII International Congress of Ophthalmology, died after a long illness in his summer home at Wiscasset, Maine on Sunday, August 26, 1959. He was 80 years of age.

In addition to serving in the highest councils of his profession, Dr. Samuels was Professor Emeritus of Ophthalmology at Cornell University Medical College and Consulting Surgeon and Pathologist at the New York Eye and Ear Infirmary. He was a member of the Board of Directors of the National Society for the Prevention of Blindness, an advisor to the Pan American Association of Ophthal-



BERNARD SAMUELS, M.D.
1879-1959

mology, and the founder of the Institute of Ophthalmology of the Americas, a postgradute teaching division of the New York Eye and Ear Infirmary for Latin American ophthalmologists.

For many years, Dr. Samuels represented the United States on the International Council of Ophthalmology and was responsible for bringing the XVII Congress to New York City in the fall of 1954. His efforts were rewarded by his being elected president of the congress.

In 1927, he was Chairman of the Section of Ophthalmology of the New York Academy of Medicine, in 1947, Vice-President of the American Academy of Ophthalmology and Otolaryngology, and in 1948, he was elected President of the

American Ophthalmological Society. He also was a member of the Alpha Kappa Kappa and Alpha Omega Alpha Societies.

Dr. Samuels was known throughout the world as an excellent clinician, renowned scientific writer, inspired teacher, and great humanitarian.

Most of Dr. Samuels' clinical work was performed at the New York Eye and Ear Infirmary and the Cornell University Medical School. He began his career under the tutelage of the late Dr. Robert G. Reese, who was in charge of a clinic at the Infirmary and Professor of Ophthalmology at the University. His appointments at both institutions began in 1914 and extended until his retirement in 1942, interrupted by his service as a major in the medical corps in the American Expeditionary Forces in France in 1917-18. On returning from military service, Dr. Samuels opened his own office and enjoyed one of the largest practices in New York. It was not unusual for him to see 70 or 80 patients in his office in the morning and spend the afternoon in his clinic at the Infirmary, or teaching undergraduate students in the medical school. He took particular pride in the surgical record of his clinic at the Infirmary. On one record breaking occasion more than 30 major operations were performed in one afternoon by him and his staff. He retained and prized a photostatic copy of the operating schedule of that memorable day. It was a privilege to attend rounds and conferences with him. Young ophthalmologists often waited for hours to accompany him on his visits to patients on the wards.

Although Dr. Samuels was well grounded in the humanities, he was especially informed on the history of ophthalmology, and became one of the most prolific writers on scientific and historical subjects. He had the ability to describe conditions in brief concise terms which he said was due to his training under the late Dr. Arnold Knapp, then editor of the ARCHIVES OF OPHTHALMOLOGY. Like many of the secretaries of the Section of Ophthalmology of the New York Academy of Medicine, Dr. Samuels was requested by Dr. Knapp to revise and condense his reports for the Archives on more than one occasion. This training led to the editorship of the Transactions of the American Ophthalmological Society for many years. He wrote numerous articles dealing with pathology of the eye and concluded his work with Prof. Adalbert Fuchs by writing an authoritative text book, "Clinical Pathology of the Eye," published by Harper & Brothers, in 1952.

In preparation for his teaching experience, Dr. Samuels received his medical degree in 1907 from the Jefferson Medical College in Philadelphia, and served general internship in St. Mary's Hospital, Pueblo, Colorado. This was followed by postgraduate studies in ophthalmology in the university clinics of Vienna, Prague, and Berlin. He became a faithful disciple of the late Professor Ernest Fuchs and brought his teaching methods back to America for the benefit of western ophthalmology. Immediately on his return from military service in 1919, Dr. Samuels with the aid of Dr. Edgar Burchell established the first organized course of "Histopathology of the Eye" in the New York area. Through his connections with European ophthalmologists, he was able to procure at his own expense several collections of valuable teaching slides which are still in use in the postgraduate course at the Infirmary. Through his and Dr. Burchell's efforts, the collection of teaching slides at the Infirmary became one of the largest and most important in the world. With this wealth of material, Dr. Samuels was able to introduce histopathology of the eye in the undergraduate curriculum of Cornell University Medical School. The novelty became so popular that some students

would skip other classes to hear him lecture. At the Infirmary, doctors from all parts of the world enrolled in his classes for postgraduate training in pathology of the eye. About the time Dr. Samuels established his course in New York, Dr. Georgiana Theobald of Chicago, Dr. Frederick Verhoeff of Boston, and the late Dr. Jonas Friedenwald of Baltimore started similar courses. They collaborated frequently on this phase of ophthalmology, and made histopathology a basic requirement for training in the specialty.

Not only was Dr. Samuels well versed in medical history, but he took an active interest in the activities of the New York Historical Society. He knew the history of his native Virginia and the United States as few of this age know it. He was a member of the St. Nicholas Society, the Sons of the Revolution, the Veterans of Foreign Wars, the Century Club, and the Southern Society. He collected historical objects of art, old books and paintings, and had an original bust of Washington by Houdon. He established a library adjoining his home in Front Royal, Virginia. It was through his influence and support that the portraits of the founders and their successors were preserved at the Infirmary. He saved old records and guarded antique and modern books at the Infirmary so well that the Library was named in his honor in a special ceremony.

In 1957, Dr. Samuels, with the aid of the Board of Surgeons and Directors of the New York Eye and Ear Infirmary, established the Institute of Ophthalmology of the Americas. In this enterprise, he had the support of the late Dr. Moacyr Alvaro of São Paulo, Brazil, Executive Director and past President of the Pan American Association of Ophthalmology. The institute has been highly successful and enjoys patronage from many Latin American countries and the United States.

For many years, Dr. Samuels supported campaigns to rebuild the Infirmary at its present location, but unfortunately he did not live to see actual accomplishment.

In retrospect, Dr. Bernard Samuels was born in Front Royal, Virginia in 1879, received his basic and medical education in the United States and postgraduate training in Europe, became one of the leading clinicians of New York, and one of the great teachers and writers of his time. Although he never married, he was interested in the families of the young men who trained under his direction. He enjoyed his friendships with former students and often helped them in his quiet unassuming manner. Although he must have been lonely at times, no one ever knew about it. Whatever he did, it was for the best as he saw it. The world and ophthalmology have gained for having had the services of Bernard Samuels.

BRITTAIN F. PAYNE, M.D.

News and Comment

ANNOUNCEMENTS

Asia-Pacific Academy of Ophthalmology.—The Asia-Pacific Academy of Ophthalmology will meet in Manila, Oct. 10 to 13, 1960. The principal subject of this meeting will be "Blinding Diseases in Asia." Under this heading, cataract, glaucoma, diseases of the cornea, trachoma, and nutritional deficiencies of the eye will be discussed.

Ophthalmologists interested in presenting papers should contact Dr. William John Holmes, Secretary General, 1013 Bishop St., Honolulu 13, Hawaii.

Those interested in attending the meeting may obtain further information from the Compass Travel Bureau, Inc., 55 W. 42d St., New York 36.

Postgraduate Course in Ophthalmology.—The Department of Ophthalmology of the State University of New York Upstate Medical Center at Syracuse will present its Tenth Annual Postgraduate Course in Ophthalmology at the Hotel Syracuse, Friday and Saturday, Dec. 4th and 5th, 1959.

The following lecturers will participate: Drs. A. B. Reese, A. Gerard DeVoe, and J. Gordon Cole.

The tuition fee is $25, payable to the State University of New York Upstate Medical Center at Syracuse, 766 Irving Ave., Syracuse 10, N.Y. This fee covers tuition, daily luncheons, and dinner on Friday night. The course will be limited to 60 members. These will be accepted in the order in which applications, accompanied by checks, are received. Inquiries regarding the course may be addressed to James L. McGraw, M.D. at the same address.

Course for Orthoptic Technicians.—The Division of Ophthalmology of the Baylor University College of Medicine offers its facilities for the training of orthoptic technicians. This program is open to any young woman who has completed successfully at least two years of college or who is a graduate nurse. Good health and vision are required of the trainees.

The course consists of 12 months didactic and practical training. Didactic training, which consists of lectures on refraction, retinoscopy, physiological optics, perimetry, ocular anatomy, neuroanatomy and motility, will be given by members of the Division of Ophthalmology. Practical training will consist of working in a clinic under the supervision of a certified orthoptic technician.

At the completion of the training, students are eligible to take the board examinations for certification by the American Orthoptic Council.

There is no tuition for the course. Students will be required to provide their own living arrangements. Limited financial assistance is available through the Delta Gamma Fraternity, (Mrs. Ronald J. Foulis, National Project Chairman, 4432 Edmunds St. N.W., Washington, D.C.)

A personal interview is required of each applicant. For information write:

Louis J. Girard, M.D., Head, Division of Ophthalmology
Baylor University College of Medicine
712 Hermann Professional Building
Houston 25, Texas

Institute of Ophthalmological Documentation.—This Institute, organized by the French Society of Ophthalmology and the Faculty of Medicine of Paris, was opened on March 1st in the premises of the former Faculty of Medicine, 12, Rue de l' Ecole de Médecine (stairs "A", 1st floor).

Visiting hours are week-days, from 9:30 to 12 a.m. and 2 to 6 p.m. Saturday, 9:30 to 12 a.m.

Among the various works are collections of French and foreign periodicals and ophthalmological books, including many ancient ones, not to be found elsewhere.

Ophthalmologists not living in Paris may obtain microfilms from the Faculty.

The Institute of Documentation is opened to physicians and medical students interested in ophthalmology.

Ophthalmic Pathology Club.—The first meeting of the Midwestern Section of the Ophthalmic Pathology Club will be on Saturday, Jan. 16, 1960, in Iowa City. The meeting is open to anybody interested in ophthalmic pathology. For further details, please contact F. C. Blodi, M.D., University Hospitals, Iowa City, Iowa.

Post Pan-American Congress Meeting in New York.—The Institute of Ophthalmology of the Americas will conduct a post Pan-American Congress Meeting at the New York Eye and Ear Infirmary from Feb. 9-17, 1960. Each Symposium will be composed of two Latin-American Ophthalmologists and two Infirmary Staff Members. The schedule is as follows:

Tuesday, Feb. 9, 1960 10-Noon	Cataracts
Wednesday, Feb. 10, 1960 10-Noon	Retinal Detachment
Thursday, Feb. 11, 1960 10-Noon	Muscle Anomalies
Friday, Feb. 12, 1960 10-Noon	Glaucoma
Saturday, Feb. 13, 1960 10-Noon	Uveitis
Monday, Feb. 15, 1960 10-Noon	Keratectomies and Keratoplasties
Tuesday, Feb. 16, 1960 10-Noon	Pleoptics and Macular Function Testing
Wednesday, Feb. 17, 1960 9-5	Surgical Demonstrations on TV

Invitations to attend may be obtained by writing to Mrs. Tamar Weber, Registrar, Institute of Ophthalmology of the Americas, New York Eye and Ear Infirmary, 218 Second Ave., New York 3, N.Y.

National Council to Combat Blindness, Inc.—The National Council to Combat Blindness, Inc., announces 1959 Fight For Sight awards to medical colleges, hospitals, research centers, and individual investigators totaling $160,000. These awards include 26 grants-in-aid, eight postdoctoral fellowships, two predoctoral fellowships, 20 summer student fellowships and three awards in support of clinical service projects.

Fight For Sight grants-in-aid and full-time research fellowships are generally awarded for a period of one year and may be renewed with the approval of the National Council to Combat Blindness' Scientific Advisory Committee.

The organization announces an increase in its stipend allowance for research fellowships. Formerly the stipend range was from $2,400 to $5,000 per year. The newly established range is from $3,600 to $7,500. Student fellowship stipends have also been increased with the maximum allowance now set at $300 per month. Student fellowships are awarded for a two or three month period.

Jan. 1, 1960, has been designated as the closing date for receipt of applications for the 1960-61 group of awards from applicants not requesting renewal support. Applicants (other than those filing for student fellowships) who wish to apply for continuation support are requested to file no later than March 15. Appropriate forms may be obtained by addressing: Secretary, National Council to Combat Blindness, Inc., 41 W. 57th St., New York 19.

Seven additional members have joined the Scientific Advisory Committee of the organization: Herman M. Burian, M.D., Professor, Department of Ophthal-

mology, State University of Iowa, College of Medicine, Iowa City; W. Morton Grant, M.D., Associate Professor of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Cambridge, Mass.; V. Everett Kinsey, Ph.D., Assistant Director of Research, Kresge Eye Institute, Detroit, Michigan; John McClean, M.D., Chief, Department of Ophthalmology, New York Hospital-Cornell Medical Center, New York; Edward W. Norton, M.D., Chairman, Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida; George H. Smelser, Ph.D., Department of Ophthalmology, Columbia University College of Physicians and Surgeons, New York, and Bradley R. Straatsma, Chief, Division of Ophthalmology, Department of Surgery, University of California Medical Center School of Medicine, Los Angeles.

Other members of the Committee are: Charles A. Perera, M.D., Chairman, Scientific Advisory Committee and Associate Professor of Ophthalmology, Columbia University College of Physicians and Surgeons, New York; James H. Allen, M.D., Chief, Department of Ophthalmology, Tulane University School of Medicine; Bernard Becker, M.D., Chief, Department of Ophthalmology, Washington University School of Medicine; Frederick Crescitelli, Ph.D., Department of Zoology, University of California; Arthur G. DeVoe, M.D., Chairman, Department of Ophthalmology, Columbia University College of Physicians and Surgeons, New York; Dan M. Gordon, M.D., Assistant Professor, Department of Ophthalmology, New York Hospital-Cornell Medical Center; Charles Haig, Ph.D., Associate Professor, Department of Physiology and Pharmacology, New York Medical College, New York; Michael J. Hogan, M.D., Director, Francis I. Proctor Foundation, University of California Medical School; Peter C. Kronfeld, Head, Department of Ophthalmology, University of Illinois College of Medicine, Chicago; Irving H. Leopold, M.D., Director of Research, Wills Eye Hospital, Philadelphia; A. E. Maumenee, M.D., Director, Department of Ophthalmology, Johns Hopkins University Medical School, Baltimore; Stuart Mudd, M.D., Professor, Department of Microbiology, University of Pennsylvania School of Medicine; Frank Newell, M.D., Chief, Department of Ophthalmology, University of Chicago Clinics; Theodore C. Ruch, Ph.D., Chairman, Department of Physiology and Biophysics, University of Washington, Seattle; Samuel L. Saltzman, M.D., Assistant Professor, Department of Ophthalmology, New York Medical College; Kenneth C. Swan, M.D., Chief, Department of Ophthalmology, University of Oregon; Phillips Thygeson, M.D., Professor of Ophthalmology, University of California Medical School, San Francisco.

PERSONAL

New Director at Armed Forces Institute of Pathology.—Colonel Frank M. Townsend, USAF, MC, has been appointed Director of the Armed Forces Institute of Pathology succeeding Captain William M. Silliphant, MC, USN. Colonel Townsend is the first Air Force Officer to assume the Directorship of the Institute.

The Armed Forces Institute of Pathology is the central laboratory of pathology for the Department of Defense. In addition to serving the Armed Services, the Institute meets the needs of the Public Health Service, The Atomic Energy Commission, Veterans Administration, other federal agencies, and civilian pathologists in the form of consultative service.

Colonel Townsend, the senior pathologist of the Air Force, also serves as the consultant in pathology to the Surgeon General, Department of the Air Force.

The new Director is a pioneer in the field of Aviation Pathology. In addition, Colonel Townsend has published numerous articles on subjects relative to aviation medicine and has presented many lectures on the subject of aviation pathology throughout the United States and abroad. He was also chairman of the Joint Committee on Aviation Pathology.

GENERAL NEWS

National Council to Combat Blindness 1959-60 Research Grants

GRANTS-IN-AID AND CLINICAL SERVICE PROJECTS

Investigator & Institution	Project Title	Amount
Adler, Francis H., M.D. & Frayer, William C., M.D. Hospital of the University of Pennsylvania, Philadelphia.	Study of the Factors Involved in the Proliferation of the Retinal Pigment Epithelium in Disease	$ 1000
Auerbach, Edgar, M.D. Hadassah University & Medical School, Jerusalem, Israel.	Impaired Vision and its Connection with Light (Color) Sense	1500
Balazs, Endre A., M.D. Retina Foundation, Boston.	Studies on the Hyaluronic Acid Formation in the Vitreous Body	4000
Baum, Gilbert, M.D. New York University, Postgraduate Medical School, New York.	A Comparison of the Acoustic Properties of Benign and Malignant Ocular Tissues	5000
Brunish, Robert, Ph.D. University of Virginia School of Medicine, Charlottesville, Va.	Characterization of the Ophthalmotrophic Hormone	6900
Campbell, Charles J., M.D. Columbia University, College of Physicians & Surgeons, New York.	The Determination of Adoptometric Thresholds of Various Regions of the Retina in Normal and Pathological Subjects and the Relation of the Thresholds to the Clinical Appearance of the Fundus	4155
Cibis, Paul A., M.D. Washington University, School of Medicine, St. Louis.	Histopathology of the Eye with Oblique Illumination	6512
Day, Robert M., M.D. Columbia University, College of Physicians & Surgeons, New York.	Exophthalmos Inhibiting Factor in Human Serum	1200
Donn, Anthony, M.D. Columbia University, College of Physicians & Surgeons, New York.	Factors Influencing the Active Transport of Sodium into the Corneal Stroma	1500
Garron, Levon K., M.D. & Foerster, Helenor Campbell Francis I. Proctor Foundation, University of California, San Francisco.	Special Histopathologic Study of Endogenous Uveitis	4500
Germuth, F. G., Jr., M.D. & Senterfit, Lawrence B. Charlotte Memorial Hospital, Charlotte, N.C.	Studies on Antigen-Antibody Reaction in the Avascular Cornea	5000
Hanna, Calvin, Ph.D. University of Vermont, Burlington, Vt.	Studies on Cataract Formation	3254
Hargens, Mr. C. W. The Franklin Institute of the State of Pennsylvania, Philadelphia.	Development, Exploration, and Application of a Glaucoma Detector Based on Induced Vibrations of the Eyeball	3000

Investigator & Institution	Project Title	Amount
Hepner, Ray, M.D. University of Maryland, School of Medicine, Baltimore.	The Effects of Maternal Hyperoxemia on the Intrauterine Development of the Eye	1750
Iser, Gilbert, M.D. University of Illinois, Chicago.	Role of the 'A' Wave in Clinical Electroretinography	3000
Jacobson, Jerry Hart, M.D. New York Eye & Ear Infirmary, New York.	Behavioral Studies of Higher Level Vision in Monkeys	5000
Kornblueth, Walter, M.D. Hadassah University Hospital, Jerusalem, Israel.	Metabolism of Orbital Fat	3800
Kornzweig, Abraham, L., M.D. Home for Aged & Infirm Hebrews of New York, New York.	The Eye in Old Age—A Clinical and Pathological Study	1250
Ley, Albert, P., M.D. Washington University, School of Medicine, St. Louis.	Histology of Zonulolysis with Alpha Chymotrypsin	4975
Lovekin, Louise G., M.D. Yale University, New Haven, Conn.	Physiological Reaction to Glass Implantation in Tissues	750
Luck, Cecil P. (Dr.) University College of East Africa, Kampala, Uganda, Africa.	Comparative Ophthalmology of Mammals, with Special Reference to Primates	4500
Sistrom, William R., Ph.D. Harvard University, Cambridge, Mass.	The Role of Carotene Pigments in the Structure and Function of the Chromatophores of Photosynthetic Bacteria	5000
Smelser, George K., Ph.D. Columbia University, College of Physicians & Surgeons, New York.	Investigations on the Pathogenesis of Experimental Exophthalmos	2400
Tsutsui, Jun, M.D. Okayama Rosai Hospital, Okayama-shi, Japan.	Immunochemical Studies of Corneal Protein in Homo- and Hetero-Corneal Graft	1400
Wolken, Jerome J., Ph.D. University of Pittsburgh, Medical Center, Pittsburgh.	Photoreceptor Structures	3132

SPECIAL GRANT

For payment to specialized personnel for the development of a scientific protocol for the investigation of 11-cis vitamin A as a therapy for retinitis pigmentosa and one which will provide future investigators with a standard procedure for the evaluation of therapies purported to be beneficial in the treatment of this disease.	4500

CLINICAL SERVICE PROJECTS

Gordon, Dan M., M.D. New York Hospital—Cornell Medical Center, New York.	For the Maintenance and Improvement of Low Vision Clinic; Application of Visual Aids in Patients with Subnormal Vision	$ 2250
Holtz, Harry M., M.D. Newark Beth Israel Hospital, Newark, N.J.	To Provide Instruments and Equipment for Tonography in Glaucoma and Suspected Glaucoma	1000
Kirsch, Ralph E., M.D. Mt. Sinai Hospital, Miami Beach, Fla.	Purchase of Equipment to Assist in the Establishment of an Eye Clinic	2500

PREDOCTORAL AND POSTDOCTORAL RESEARCH FELLOWSHIPS
1959-60

Fellow & Institution	Direct Supervisor	Project Title	Amount
Bard, Leslie A. (Mr.) Johns Hopkins Hospital, Baltimore.	Arnall Patz, M.D.	Serum Proteins in Diabetes and Diabetic Retinopathy	$ 2000
Brandt, Philip W. (Mr.) Columbia University, College of Physicians & Surgeons, New York.	George D. Pappas, Ph.D. & George K. Smelser, Ph.D.	A Study of Solute Movement Across the Endothelial-like Cells and Epithelial Cells Lining the Anterior Segment of the Eye	4400
Chulavachana, Tavisak, M.D. Tulane University, School of Medicine, New Orleans.	James H. Allen, M.D. & Earl Fisher, Jr., Ph.D.	Studies Regarding Ocular Staphylococcal Infections	4800
Hedbys, Bengt Olof, M.D. Retina Foundation, Boston.	Claes H. Dohlman, M.D.	Studies on Corneal Dehydration and Experimental Keratoplasty	5000
Holmberg, Ake Sigurd, M.D. Washington University, School of Medicine, St. Louis.	Bernard Becker, M.D.	Ultrastructure of the Ciliary Epithelium and the Trabeculum	2500
Leith, Arthur B., M.D. University of London, London, England.	Dr. E. S. Perkins	Measurement of Episcleral & Aqueous Vein Pressures in Open Angle Glaucoma	2400
Matton-Van Leuven, Maria Th., M.D. Duke University, School of Medicine, Durham, N.C.	F. W. Stocker, M.D. & N. Georgiade, M.D.	Comparative Studies, by Tissue Culture and Grafting of Viability of Animal and Human Corneas, Frozen at Various Temperatures	3600
Rohen, Johannes, W., M.D. Washington University, School of Medicine, St. Louis.	Bernard Becker, M.D.	Experimental Studies on the Histology of the Trabecular Meshwork	5000
Tokunaga, Tsugihiko, M.D. State University of Iowa, University Hospitals, Iowa City.	P. J. Leinfelder, M.D.	Cytological Study in Electron Microscopy on Radiation Cataract; Study on Incipient Opacities of Experimental Cataracts	1200
Tsukahara, Isamu, M.D. Columbia University, College of Physicians & Surgeons, New York.	Algernon B. Reece, M.D.	Ophthalmic Pathology	2500

SUMMER STUDENT FELLOWSHIPS
1959

Applegate, George W. Johns Hopkins University, School of Medicine, Baltimore.	Arnall Patz, M.D.	Experimental Production of Ocular Tumors and Surface Epithelial Downgrowths in the Animal Eye	$ 600

Fellow & Institution	Direct Supervisor	Project Title	Amount
Bean, William J. Tulane University, School of Medicine, New Orleans.	Fred W. Schueler, Ph.D. Monte G. Holland, M.D.	Re-examination of the Physiology of Aqueous Humor Kinetics: Application of Newly Developed Techniques on the Study of Aqueous Humor Kinetics to Ophthalmic Pharmacology	600
Bergland, John Johns Hopkins University, School of Medicine, Baltimore.	A. E. Maumenee, M.D.	Investigations in Ocular Hypersensitivity	600
Burda, Christopher D. Tulane University, School of Medicine, New Orleans.	Earl Fisher, Jr., Ph.D.	Experimental Fungal Keratitis in Rats	600
Burket, John M. State University of Iowa, College of Medicine, Iowa City.	Ralph C. Janes, Ph.D.	Histological Studies of the Iris with Especial Consideration of the Dilator Fibers. Comparison of Animals and Man Using Various Techniques	400
Christy, Rosa Mae University of California, Medical Center, San Francisco.	I. W. Monie, M.B., Ch.B. (Glas)	Histochemical Study of the Distribution of Acid Mucopolysaccharides, Carbohydrates, and Lipids in the Anterior Segment of the Rat Eye	600
Feller, Martin R. State University of New York, Downstate Medical Center, New York.	Bernard Schwartz, M.D.	Temperature Gradients in the Rabbit Eye	550
Franklin, Ernest W., III Charlotte Memorial Hospital, Charlotte, N.C.	Frederick G. Germuth, Jr., M.D.	Studies of Antigen-Antibody Reactions in the Avascular Cornea	600
Hopkins, David R. Retina Foundation, Boston.	Torvard C. Laurent, M.D.	Interaction Between Collagen and Other Macromolecules in Collagen Gels	400
Leibowitz, Howard, M.I. Johns Hopkins University, School of Medicine, Baltimore.	James J. Parks, Ph.D.	Investigations in Ocular Hypersensitivity	600
Metz, Henry S. State University of New York, Downstate Medical Center, New York.	Donald M. Kirschenbaum, Ph.D.	Determination of the Proteolytic Activity of the Lens of the Eye	600
O'Brien, James E., Ph.D. University of Vermont, College of Medicine, Burlington, Vt.	Calvin Hanna, Ph.D.	Intracellular Biochemical Changes in the Gamma Ray Treated Eye	600
Overby, John L. Tulane University, School of Medicine, New Orleans.	Earl Fisher, Jr., Ph.D.	Immunochemical Analysis of Corneal Proteins. (I. Comparison of Various Animal Species)	600

Fellow & Institution	Direct Supervisor	Project Title	Amount
Schafrank, Michael S. State University of New York, Downstate Medical Center, New York.	Bernard Schwartz, M.D.	Changes in the pH of the Aqueous of the Enucleated Rabbit Eye with Time	600
Shin, Ernest Eun-Ho Eye and Ear Hospital, University of Pittsburgh, Pittsburgh.	Jerome J. Wolken, Ph.D.	Physicochemical Mechanism of Energetics in Photoreception, with Main Emphasis on Energy Transfer. Energy Transfer in Photoreceptor of *Euglena Gracilis*	600
Stiles, James F. State University of Iowa, College of Medicine, Iowa City.	Ralph C. Janes, Ph.D.	The Penetration of Radio Labeled Cortisone and Hydrocortisone in Normal Eyes with Certain Pathological Abnormalities	600
Sugiki, Shigemi Washington University, School of Medicine, St. Louis.	Bernard Becker, M.D.	Tissue Culture of the Ciliary Body Epithelium. Effects of Cyanide, Anoxia, Carbonic Ahydrase Inhibitors, etc.	600
Watanabe, Saeko Okayama Rosai Hospital, Japan.	Jun Tsutsui, M.D.	Electrophoretic Analysis of Corneal Protein. Comparative Analysis of Corneal Protein Fraction in Different Kinds of Animal Species	250
Witkovsky, Paul University of California, Los Angeles.	Frederick Crescitelli, Ph.D.	Attempt to Correlate Electroretinographic Responses with Retinal Development Using the Embryonic Chick; to Begin with a Systematic Examination (Histologically) of the Developing Retina at Various Time Intervals	600
Zweifach, Philip H. Cornell University, Medical College, New York.	Miles A. Galin, M.D.	Alterations in Intraocular Pressure Induced by Blood Osmolol Changes	600

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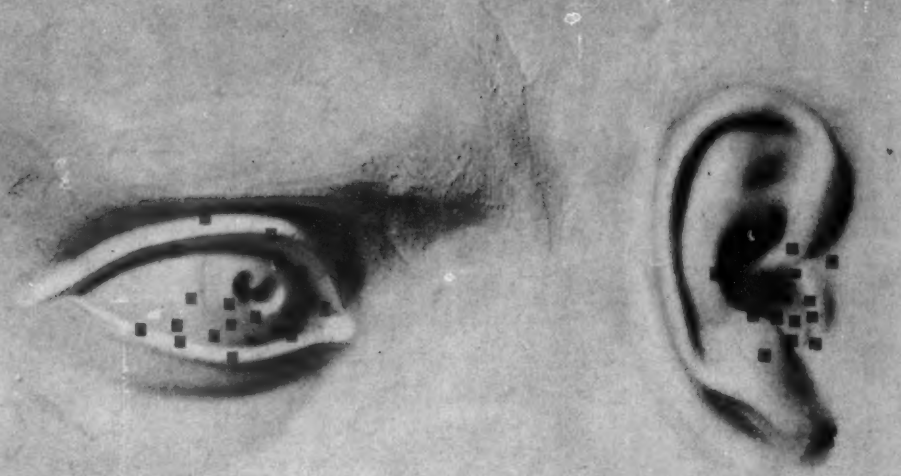

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*Baer, R. L., and Witten, V. H.: Editorial Comment. *In* The Year Book of Dermatology and Syphilology (1958-1959 Year Book Series), Edited by Rudolph L. Baer and Victor H. Witten, Chicago, The Year Book Publishers, 1959, p. 40.

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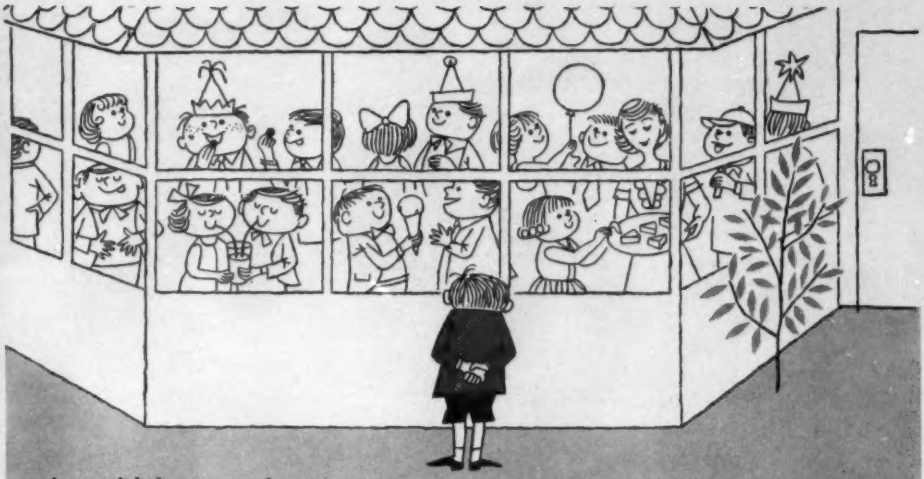

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1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.

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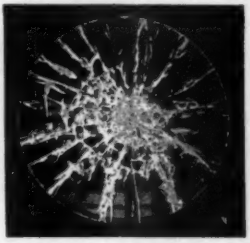

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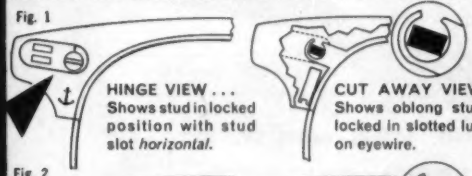
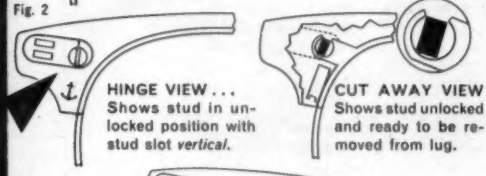
Fig. 1



HINGE VIEW . . . Shows stud in locked position with stud slot *horizontal.*

CUT AWAY VIEW Shows oblong stud locked in slotted lug on eyewire.

Fig. 2



HINGE VIEW . . . Shows stud in unlocked position with stud slot *vertical.*

CUT AWAY VIEW Shows stud unlocked and ready to be removed from lug.

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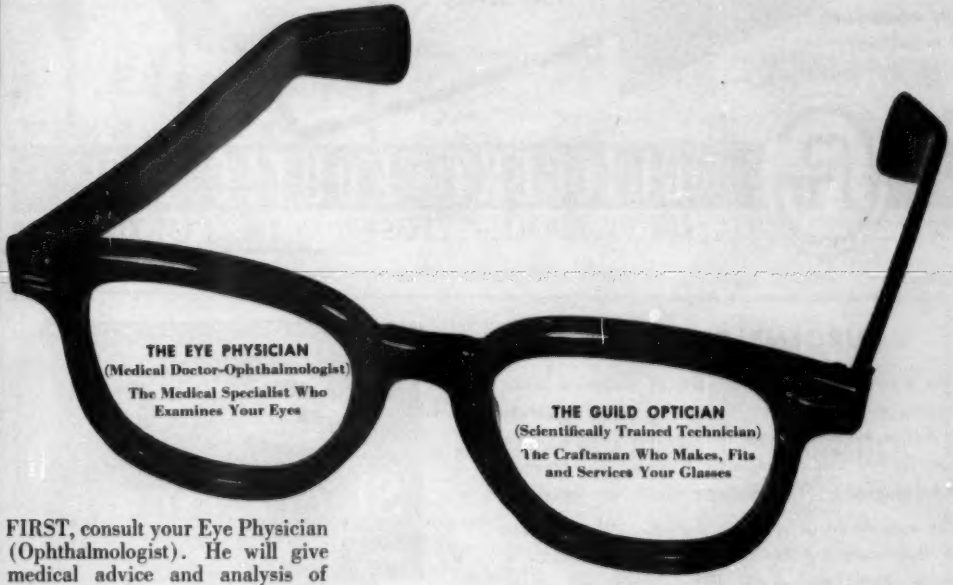
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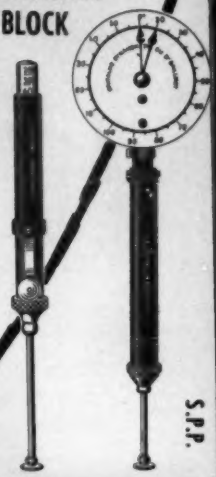

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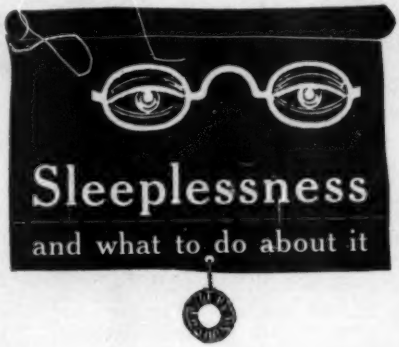

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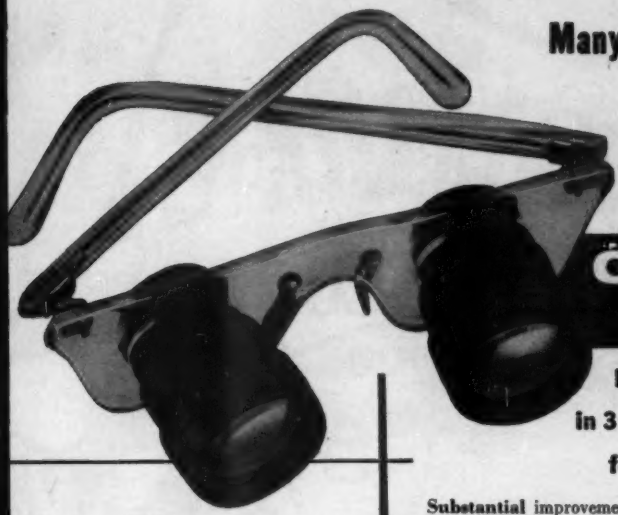

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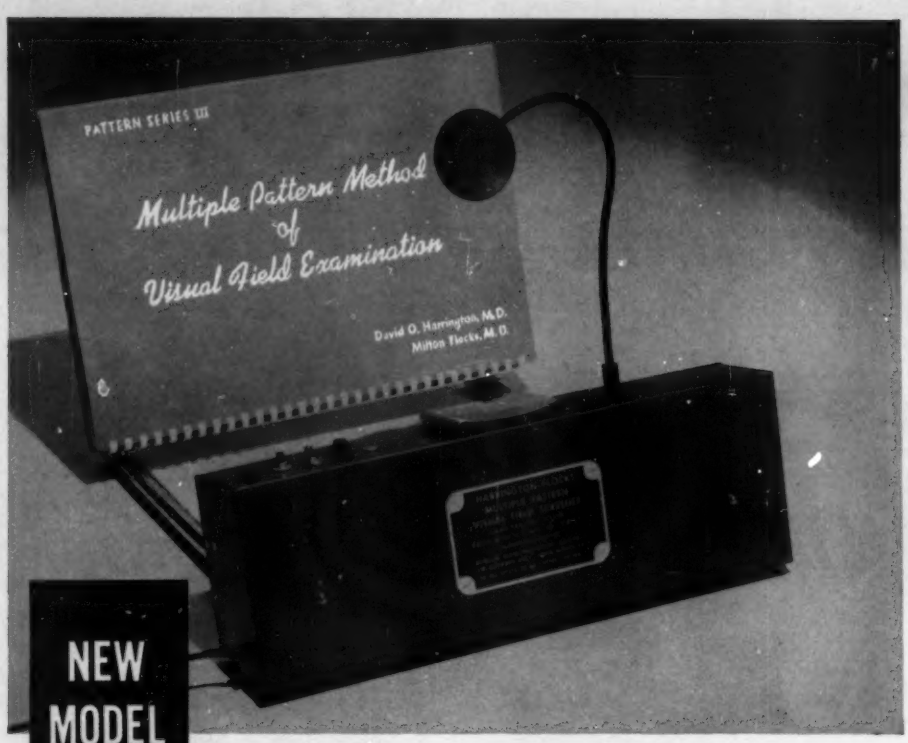

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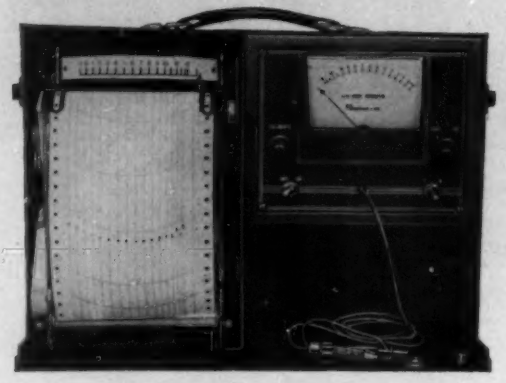

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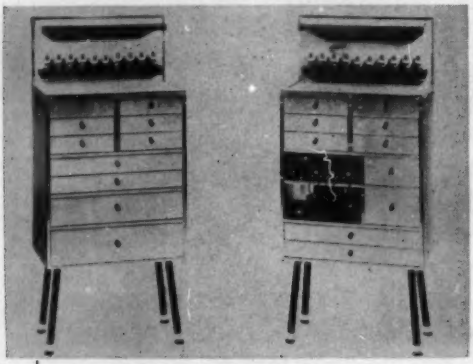

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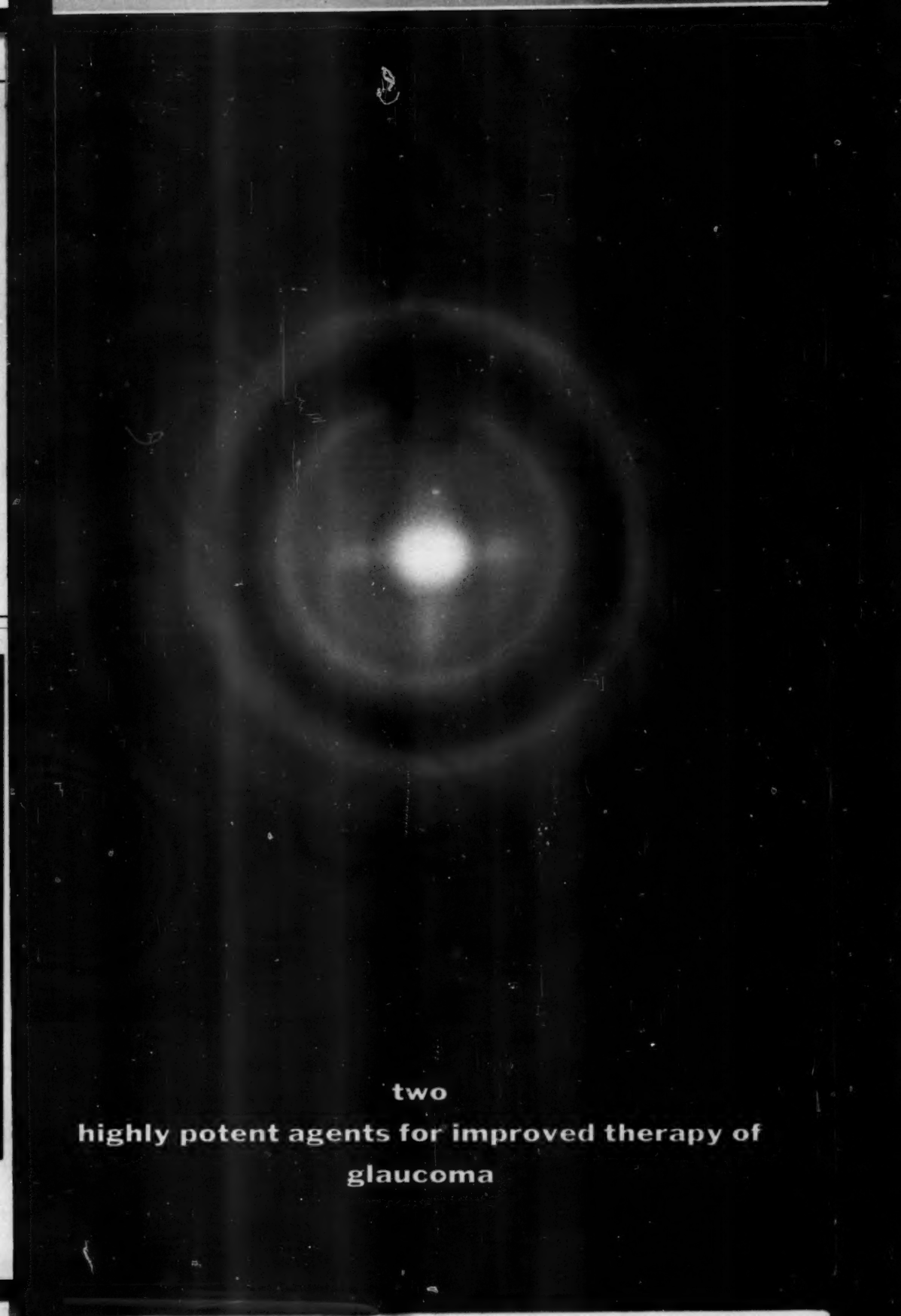
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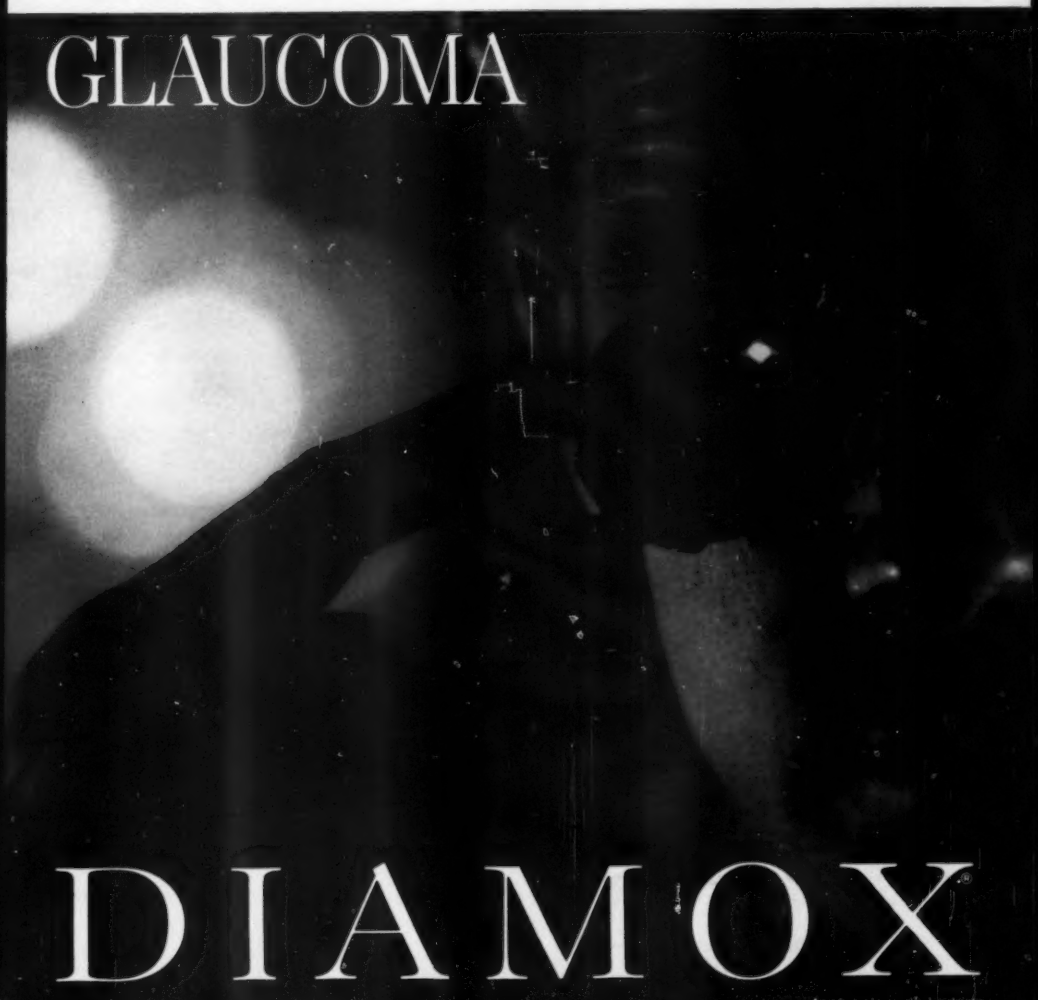
1. Venable, H. P.: J. Nat. M. A., 50:79, 1958.



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